

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202971Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # N 202971

SUPPL #

HFD # 130

Trade Name ABILIFY MAINTENA

Generic Name aripiprazole extended-release injectable suspension for intramuscular (IM) injection
300 mg/vial and 400 mg/vial.

Applicant Name Otsuka Pharmaceutical Co., Ltd.

Approval Date, If Known 2/28/2013

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒

NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒

NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

Maintenance treatment of schizophrenia.

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 21-436	Abilify tablets 2mg, 5mg, 10mg, 15mg, 20mg, 30mg
NDA# 21-729	Abilify orally disintegrating tablets 10mg, 15mg
NDA# 21-713	oral solution 1mg/mL
21-866	injectable formulation 9.75mg/1.3mL

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Trial #3107246

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a

similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Trial #3107246

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND # 67,380	YES <input checked="" type="checkbox"/>	! NO <input type="checkbox"/>
		! Explain:

Investigation #2		!
		!
IND #	YES <input type="checkbox"/>	! NO <input type="checkbox"/>
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1		!
		!
YES <input type="checkbox"/>		! NO <input type="checkbox"/>

Explain:

! Explain:

Investigation #2

!

!

YES ☐

! NO ☐

Explain:

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐

NO ☒

If yes, explain:

=====

Name of person completing form: Sonny Saini, Pharm.D., MBA

Title: Regulatory Project Manager

Date: 2/28/2013

Name of Office/Division Director signing form: Mitchell V. Mathis, M.D.

Title: Director (acting), Division of Psychiatry Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SANDEEP S SAINI
02/28/2013

MITCHELL V Mathis
02/28/2013

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 202971 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: ABILIFY MAINTENA Established/Proper Name: aripiprazole for extended-release injectable suspension Dosage Form: injectable suspension for IM use		Applicant: Otsuka Pharmaceutical Co. Agent for Applicant (if applicable):
RPM: Sonny Saini		Division: OND/ODE1/DPP
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p><u>NDA and NDA Efficacy Supplements:</u></p> <p>NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p> </div> <div style="width: 50%;"> <p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> This application does not reply upon a listed drug. <input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> This application relies on (explain)</p> <p style="color: red;"><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p> </div> </div>		
❖ Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is <u>2/28/13</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions (<i>specify type and date for each action taken</i>) 		<input type="checkbox"/> None CR - 7/26/12

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

² For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p>	<input type="checkbox"/> Received
<p>❖ Application Characteristics ³</p>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): atypical antipsychotic</p> <p> <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC </p> <p> NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies </p> <p> <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request </p> <p> BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies </p> <p> REMS: <input checked="" type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> MedGuide w/o REMS <input type="checkbox"/> REMS not required </p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<input type="checkbox"/> Yes, dates
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<p>❖ Public communications (<i>approvals only</i>)</p>	
<p>• Office of Executive Programs (OEP) liaison has been notified of action</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<p>• Press Office notified of action (by OEP)</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<p>• Indicate what types (if any) of information dissemination are anticipated</p>	<input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

☐ Yes ☐ No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

☐ Yes ☐ No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

☐ Yes ☐ No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<p align="center">CONTENTS OF ACTION PACKAGE</p>	
<p>❖ Copy of this Action Package Checklist⁴</p>	<p>Yes</p>
<p align="center">Officer/Employee List</p>	
<p>❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)</p>	<p><input checked="" type="checkbox"/> Included</p>
<p>Documentation of consent/non-consent by officers/employees</p>	<p><input checked="" type="checkbox"/> Included</p>
<p align="center">Action Letters</p>	
<p>❖ Copies of all action letters (<i>including approval letter with final labeling</i>)</p>	<p>Action(s) and date(s) CR - 7/26/12 AP - 2/28/13</p>
<p align="center">Labeling</p>	
<p>❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)</p>	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	<p>2/12/13</p>
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<p>9/26/11</p>
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	

⁴ Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input checked="" type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	2/12/13
<ul style="list-style-type: none"> Original applicant-proposed labeling 	9/26/11
<ul style="list-style-type: none"> Example of class labeling, if applicable 	
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> Most-recent draft labeling 	
❖ Proprietary Name <ul style="list-style-type: none"> Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) Review(s) (<i>indicate date(s)</i>) Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name. 	ABILIFY MAINTENA - acceptable - 1/11/13
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	<input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEPA 5/18/12, 2/11/13 <input checked="" type="checkbox"/> DMPP/PLT (DRISK) 7/3/12 <input checked="" type="checkbox"/> ODPD (DDMAC) 6/29/12 <input checked="" type="checkbox"/> SEALD 7/12/12 <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁵/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	11/21/11
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> If yes, Center Director's Exception for Review memo (<i>indicate date</i>) If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> Date reviewed by PeRC <u>5/9/12</u> If PeRC review not necessary, explain: _____ Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable

⁵ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Outgoing communications (<i>letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons</i>)	10/4/11, 11/21/11, 12/1/11, 12/2/11, 2/21/12, 4/19/12, 4/24/12, 5/24/12, 6/29/12, 7/2/12, 7/3/12, 7/26/12, 8/8/12, 9/10/12, 2/11/13, 2/12/13
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg 5/9/11
• EOP2 meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg 9/9/09
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 7/5/12
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None
Clinical Information⁶	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	
• Clinical review(s) (<i>indicate date for each review</i>)	5/30/12, 6/16/12
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	See Clinical Review - 5/30/12
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input type="checkbox"/> None CDRH 3/5/12
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input type="checkbox"/> Not applicable
❖ Risk Management	
• REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>)	
• REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)	
• Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	<input type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested 6/19/12

⁶ Filing reviews should be filed with the discipline reviews.

Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (indicate date for each review)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	<input type="checkbox"/> None
Statistical Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None
Statistical Review(s) (indicate date for each review)	<input type="checkbox"/> None 6/4/12
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None
Clinical Pharmacology review(s) (indicate date for each review)	<input type="checkbox"/> None 6/4/12
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)	<input type="checkbox"/> None 6/19/12
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input type="checkbox"/> None
• Supervisory Review(s) (indicate date for each review)	<input type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input type="checkbox"/> None 7/2/12
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input type="checkbox"/> No carc 6/4/12
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)	<input type="checkbox"/> None requested 6/19/12
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	<input type="checkbox"/> None
• Branch Chief/Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews (indicate date for each review)	<input type="checkbox"/> None 5/22/12, 5/30/12, 7/20/12, 2/19/13
❖ Microbiology Reviews	<input type="checkbox"/> Not needed 7/19/12, 2/19/13
<input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (indicate date of each review)	
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) (indicate date of each review)	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)	<input type="checkbox"/> None

❖ Environmental Assessment (check one) (original and supplemental applications)		
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)		9/26/11
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)		
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)		
❖ Facilities Review/Inspection		
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁷</i>)		Date completed: 7/20/12, 1/30/13 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (<i>date of most recent TB-EER must be within 30 days of action date</i>) (<i>original and supplemental BLAs</i>)		Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation (<i>check box only, do not include documents</i>)		<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)

⁷ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication **AND** a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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/s/

SANDEEP S SAINI
02/28/2013

Saini, Sonny

From: Saini, Sonny
Sent: Monday, February 11, 2013 3:00 PM
To: 'Goldberger, David'
Cc: Saini, Sonny; Rimmel, Sandra J
Subject: N 202971 labeling comments

Hello David,

Below are comments on carton labeling, insert labeling, QRG, and IFU for N 202971. Please resubmit with the revisions made.

A. Abilify Maintena Container Labels

The information on the container labels is very difficult to read because the labels are clear and the glass vials are translucent and clear as well. This decreases the readability of the print on the vial label. We recommend the use of a non-clear vial label that provides sufficient contrast between the text and background color so that the information on the labels can be easily read.

B. Insert Labeling, Quick Reference Guide, and Instructions for Use

One or both of the following statements regarding the excess amount of SWFI remaining in the vial were added to sections 2.4 and 2.5 of the insert labeling as well as the Quick Reference Guide and Instructions for Use:

- “The vial will have excess Sterile Water for Injection (b) (4); discard vial with the unused portion.”
- “Residual Sterile Water for Injection will remain in the vial following withdrawal (b) (4); discard vial with the unused portion.”

The use of dashes in the statements as well as omission of the unit of measure following the number 3 are error prone because the use of dashes and omission of the unit of measure may cause (b) (4) to be misread or misinterpreted as (b) (4), especially if the font size is small. Additionally, the use of (b) (4) may be misread as the amount of SWFI that should be used for reconstitution; therefore, we recommend its removal.

We recommend revising the statements as follows:

- “The vial will have excess Sterile Water for Injection; discard any unused portion.”
- “Residual Sterile Water for Injection will remain in the vial following withdrawal; discard any unused portion.”

Thanks,

Sonny

Sonny Saini, Pharm.D., MBA
CDR, USPHS
Senior Regulatory Project Manager
FDA/CDER/OND/ODE1/DPP
Phone: 301-796-0532
sonny.saini@fda.hhs.gov

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/s/

SANDEEP S SAINI
02/11/2013



NDA 202971

**ACKNOWLEDGE –
CLASS 2 RESPONSE**

Otsuka Pharmaceutical Company, Ltd.
c/o Otsuka Pharmaceutical Development & Commercialization, Inc.
Attention: David Goldberger, R.Ph., RAC
Senior Director, Regulatory Affairs
2440 Research Blvd.
Rockville, MD 20850

Dear Mr. Goldberger:

We acknowledge receipt on August 31, 2012, of your August 30, 2012, resubmission of your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Abilify Maintena (aripiprazole extended release suspension for injection) 300 mg/vial and 400 mg/vial.

We consider this a complete, class 2 response to our July 26, 2012, action letter. Therefore, the user fee goal date is February 28, 2013.

If you have any questions, call Sonny Saini, Regulatory Project Manager, at (301) 796-0532.

Sincerely,

{See appended electronic signature page}

Sonny Saini, Pharm.D., MBA
CDR, USPHS
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

SANDEEP S SAINI
09/10/2012

Saini, Sonny

From: Saini, Sonny
Sent: Friday, June 29, 2012 6:30 PM
To: 'Goldberger, David'
Cc: Laughren, Thomas P; Saini, Sonny
Subject: N 202,971 ABILIFY MAINTENA labeling revisions

Attachments: NDA 202971 Abilify Maintena PI 06 29 12.doc

Hi David,

Attached is the labeling for ABILIFY MAINTENA that includes our revisions. We should have additional revisions to the MedGuide next week. Please review and send us any comments you have on the labeling by Fri. 7/6.

Thanks,



NDA 202971 Abilify
Maintena PI...

Sonny

Sonny Saini, Pharm.D., MBA
CDR, USPHS
Senior Regulatory Project Manager
FDA/CDER/OND/ODE1/DPP
Phone: 301-796-0532
sonny.saini@fda.hhs.gov

177 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

SANDEEP S SAINI
07/02/2012

Saini, Sonny

From: Saini, Sonny
Sent: Thursday, May 24, 2012 2:46 PM
To: 'Goldberger, David'
Cc: Saini, Sonny
Subject: N 202,971 labeling comments

Hello David,

We are reviewing your proposed labeling for Abilify Maintena and would like to call your attention to section 6 (ADVERSE REACTIONS) in that document. Most of the safety analyses which you propose to describe in this section are based on the randomized, double-blind phase of trial 31-07-246. This is problematic because that phase included only patients who had tolerated and experienced a response to several weeks of treatment with both oral and IM depot aripiprazole. In addition, there was a substantial difference in follow-up times between the drug and placebo treatment groups during this phase, making a comparison of safety between the treatment groups unreliable. Therefore, the safety analyses that used these data are considered misleading for purposes of labeling.

Please propose alternative text and data displays for this section to characterize the adverse reaction experience with Abilify Maintena in a manner that can be meaningfully interpreted. If you feel that the safety profile of Abilify Maintena is very similar to that of oral Abilify formulations, this section may rely heavily on adverse reaction information contained in oral Abilify labeling. Of course, the information regarding injection site reactions should be retained and text pertaining to indications other than schizophrenia that are approved for the oral or immediate-release IM product as well as pediatric use should be removed.

The submission of your revision of section 6 in a prompt manner will assist us in completing the review of your application.

Regards,

Sonny

Sonny Saini, Pharm.D., MBA
CDR, USPHS
Senior Regulatory Project Manager
FDA/CDER/OND/ODE1/DPP
Phone: 301-796-0532
sonny.saini@fda.hhs.gov

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/s/

SANDEEP S SAINI
05/24/2012

From: Saini, Sonny
Sent: Wednesday, May 23, 2012 9:24 AM
To: 'Goldberger, David'
Cc: Saini, Sonny
Subject: N 202,971 labeling and carton/container labeling comments

Hello David,

We have the following comments regarding your labeling for N 202,971. Please incorporate these revisions to your labeling. If you have any questions please let me know.

A. Instructions for Use (IFU) for Aripiprazole Extended release Suspension for Injection Kit (300 mg and 400 mg)

1. Ensure the IFU on the back side of the sheet with Quick User Guide is consistent with the IFU used in the professional labeling, *Section 2.7, Full Prescribing Information*.
2. Delete trailing zeros throughout the Instructions for Use because trailing zero is a dangerous dose designation that appears on ISMP list of Error-Prone Abbreviations, Symbols, and Dose Designations. For example, "1.0 mL" may be misinterpreted as "10 mL" if the decimal point is not seen.
3. Delete the hyphen between the numeric characters and the words 'mL', "gauge", or "inch" in the kit contents (e.g., (b) (4) 21 gauge, 1.5 inch, etc.) as these hyphens may be misinterpreted and result in confusion.
4. To improve readability of the volume of diluent to add or of the final volume to injection, insert a space between the numerical characters and measurement units such as follows: 1.5 mL, 1 mL, or (b) (4).
5. Revise the word (b) (4) with the phrase "Sterile Water for Injection" throughout the IFU.
6. Replace the word "(b) (4)" with the proprietary name of the product.
7. Provide the illustrations depicting steps of the IFU in color to help to increase readability and comprehension of instructions. Currently, the gray-and-white figures are small, blend in with the background, and difficult to see, which may lead to the wrong preparation and administration techniques.
8. Revise the statement "(b) (4)" to read "Do not administer by any other route". Negative statements such as "(b) (4)" may have an opposite of the intended effect and inadvertently encourage the wrong route of administration. Thus, revising this statement to omit the incorrect route of administration such as "Do not administer by any other route" may help minimize the wrong route of administration error.
9. Add the statement "Administer once every 4 weeks" prior to Step 1, after the sentence "Inject immediately after reconstitution". We recommend addition of this statement to ensure that HCPs are aware of the dosing differences between the immediate release Abilify Injection and this product.
10. *Step 1, Preparing the Materials*
Add the statement "for obese patients" next to 2 inch needle to ensure the correct needle is used for obese patients. It is important that the correct needle is used for product administration due to shorter needle may result in subcutaneous administration of the product, which may lead to adverse events.
11. *Step 2, Determining Reconstitution Volume*
Revise the second sentence to be more concise and bolded to ensure the prominence and clarity of this important information as follows:

Important: There is more Sterile Water for Injection, USP in the vial than is needed to reconstitute Aripiprazole Extended-release Suspension for Injection”.

12. Step 3, Reconstituting Product

- a. Revise item #4 to replace the phrase “(b) (4)” with the phrase “1.5 mL” or “1.9 mL” for 300 mg strength and 400 mg strength respectively to increase the clarity of the statement.
- b. Revise item #7 to explain what steps should be taken to engage the needle safety device and include additional illustrations consistent with the Needle-Pro IFU. Although separate Needle-Pro IFU is included, healthcare practitioners may not refer to it as demonstrated in Formative and Validation Usability Studies. We recommend revising item #1 as follows (Example):

Remove the needle from the vial. Engage the safety device by using one-handed technique. Gently press the sheath against a flat surface until the needle is firmly engaged into the sheath. Visually confirm that the needle is fully engaged into the needle protection sheath.

- c. In item #10, revise the last negative sentence “(b) (4)” to read “Store the suspended product only in vials”. Negative statement such as “(b) (4)” may be misinterpreted as positive “(b) (4)” and have an opposite of the intended effect. Thus, this approach may encourage wrong storage of the medication and lead to additional errors.
- d. Add illustrations to item #13 to help with visualizing how to use syringe BD to remove the vial adapter from the package.

13. Step 4, Injecting Product

- a. Revise item #4 explaining how to attach the Hypodermic Needle-Pro to the syringe BD since this is important information. Additionally place illustrations to help visualize the process. Although separate Needle-Pro IFU is included, healthcare practitioners may not refer to it as demonstrated in Formative and Validation Usability Studies. We recommend revising item #4 as follows (Example):

Attach the selected Hypodermic Needle-Pro safety needle to the syringe BD containing the suspension for injection. Ensure the needle is firmly seated on the Needle-Pro safety device with the push and a clockwise twist, and then pull the needle cap straight away from the needle.

- b. Revise the second sentence in item #4 “(b) (4)” to read “Inject the recommended volume immediately”. The first part of this sentence is not relevant because by the time item #4 should be performed the suspension should already be in the syringe.
- c. In item #4, revise the statement “(b) (4)” to state “Do not administer by any other route”.
- d. In item #4, revise the statement “Engage the needle safety device” to refer to the above item #7 in step 3 that explains how to engage the needle safety device.

B. Quick Reference Guide (300 mg and 400 mg)

1. See Comments A.2 through A.4 and revise the QRG accordingly.
2. Add a prominent statement “Administer once every 4 weeks” to the QRG to ensure that HCPs are aware of the dosing differences between the immediate release Abilify Injection and this product.
3. Revise the statement “(b) (4)” to state “Sterile Water for Injection”.
4. Revise the word “(b) (4)” to state the proprietary name of the product.
5. Revise step 4 to include what steps should be taken if Aripiprazole Extended-release Suspension for Injection is not administered immediately as follows (Example):

“If the product not administered immediately, the reconstituted suspension is can be stored in the vial for up to 12 hours. Shake the vial vigorously for at least 1 minute to re-suspend prior to injection.”

6. Increase prominence of the needle sizes and the word “Obese” in step 8 by using bigger-size font or bolding.

C. Instructions for Use for Hypodermic Needle-Pro Syringe and Needle

1. Use only English language for the IFU for Hypodermic Needle-Pro Syringe and Needle in accordance with 21 CFR 201.15(c)(1).
2. Correct the spelling error of the word “Ensure” in section 6.2.
3. Increase the font size of the text to improve readability of the information.
4. Include illustrations to help visualizing how to attach the Needle-Pro safety needle device to the syringe.

D. Carton Labeling (300 mg per vial and 400 mg per vial)

Top Panel

1. Ensure the size of the established name is at least ½ size of the letters comprising the proprietary name and has prominence consistent with the proprietary name including type, size, color, and font in accordance with 21 CFR 201.10(g)(2).
2. Revise the presentation of the root name ‘Abilify’ from all upper case letters (ABILIFY) to title case (Abilify) to improve readability.
3. To be consistent with other lyophilized powders, add the phrase “per vial” after the product’s strength such as “300 mg per vial” and “400 mg per vial”.
4. The yellow color used to represent 300 mg strength overlaps with the color font used for Abilify (Aripiprazole) Injection. The visual similarity can lead to selection of the wrong product. Thus, revise the color font used for 300 mg, so that the carton labeling does not overlap or appear similar to Abilify Injection.
5. Add the medication guide statement to the top panel above the “Single use only” statement per 21 CFR 208.24(d). Consider using the statement as follows: “Attention: Dispense an enclosed Medication Guide to each patient”.
6. Revise the presentation of the proprietary name to appear in the same font size, color, and type size. This presentation will emphasize the full name of the product. Currently, the root name is more prominent than the modifier, which may lead to confusion if modifier is overlooked due to decreased prominence.
7. Delete the graphic of the twisted lines on the top panel as this graphic is prominent and intervenes with readability of the important information such as proprietary and established names and route of administration.
8. Increase the prominence of the route of administration by using bigger font size as this information is very important and should be emphasized.
9. To reinforce that this product is packaged in a single-use vial, add the statement “Discard Unused Portion” immediately after the statement “Single use only”.
10. If space permits, add the following table to the 300 mg strength product:

Intended Dose	Amount of diluent for reconstitution	Amount to inject by using adapter
300 mg	1.5 mL	1.5 mL
200 mg	1.5 mL	1 mL

And to the 400 mg strength:

Intended Dose	Amount of diluent for reconstitution	Amount to inject by using adapter
400 mg	1.9 mL	2 mL

If space does not permit or addition of the tables to the top panel greatly clutters the most important information such as proprietary and established names, dosage form, strength, and route of administration, add these tables to the front panel of the carton labeling.

Side Panel

1. Revise the statement “(b) (4)” to state “One (b) (4) vial of diluent: Sterile Water for Injection, USP”.
2. Delete the hyphen between the numeric characters and the words ‘mL’, “gauge”, or “inch” in the kit contents (e.g., (b) (4), 21 gauge, 1.5 inch, etc.) as these hyphens may be misinterpreted and result in confusion.
3. In the Usual Dosage, add the statement “Administer once every 4 weeks” before the statement “See Package Insert”. We recommend addition of the statement to ensure the correct dosing schedule is followed and to ensure that HCPs are aware of the dosing differences between the immediate release Abilify Injection and this product.

E. Aripiprazole Vial Label (300 mg per vial and 400 mg per vial)

1. See Comments D.1 through D.4 and revise the vial labels accordingly.
2. The different types of boxing around the strengths (i.e., black box around 300 mg strength and white box around 400 mg) do not provide sufficient differentiation between the two strengths of the product. Thus, vial labels look too similar to each other and to the diluent (i.e., Sterile Water for Injection, USP) containing black writing on the white background. As a result, the wrong strength of the product may be selected. Please provide additional differentiation between the strengths by employing different colors consistent with the carton labeling or additional means to help prevent selection errors.
3. Increase the prominence of the route of administration by using bold and/or larger font.

F. Sterile Water for Injection, USP Vial Label (Diluent)

1. Revise “(b) (4)” to state “Sterile Water for Injection, USP” as “(b) (4)” was not identified in USP monograph.
2. Delete the statement “(b) (4)” as this prominent statement may be misinterpreted that this vial actually contains the active ingredient.
3. Add the statement “For single use only” after the word “Sterile” to emphasize that the product should be used only once.

Regards,

Sonny

Sonny Saini, Pharm.D., MBA
CDR, USPHS
Senior Regulatory Project Manager
FDA/CDER/OND/ODE1/DPP
Phone: 301-796-0532
sonny.saini@fda.hhs.gov

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/s/

SANDEEP S SAINI
05/24/2012



NDA 202971

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Otsuka Pharmaceutical Company, Ltd.
c/o:
Otsuka Pharmaceutical Development & Commercialization, Inc.
1 University Square Drive, Suite 500
Princeton, NJ 08540,

ATTENTION: David Goldberger, R.Ph., RAC
Sr. Director, Regulatory Affairs

Dear Mr. Goldberger:

Please refer to your New Drug Application (NDA) dated and received September 26, 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for aripiprazole extended-release suspension for injection, 300 mg/vial and 400 mg/vial.

We also refer to your correspondence dated February 23, 2012, and received February 24, 2012, requesting review of your proposed proprietary name, Abilify Maintena.

We have completed our review of the proposed proprietary name Abilify Maintena, and have concluded that it is acceptable. If any of the proposed product characteristics as stated in your February 23, 2012, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

Additionally, this proprietary name must be re-evaluated 90 days prior to the approval of the application. The conclusions upon re-review are subject to change.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sandra Griffith, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2445. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Sandeep Saini at (301) 796-0532.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
05/22/2012

Saini, Sonny

From: Suggs, Courtney
Sent: Wednesday, May 16, 2012 10:50 AM
To: Saini, Sonny
Cc: Laughren, Thomas P; Mathis, Lisa; Addy, Rosemary; Greeley, George
Subject: NDA 202971

Attachments: 1_Pediatric_Record.pdf

Hi Sonny,

The email serves as confirmation of the review for Abilify Maintena (aripiprazole extended-release suspension for injection) for maintenance treatment of schizophrenia conducted by the PeRC PREA Subcommittee on May 9, 2012.

The Division presented a full waiver in pediatric patients because the product fails to represent a meaningful therapeutic benefit and is unlikely to be used in a substantial number of patients for the management of maintenance treatment of schizophrenia. Recruiting pediatric patients for a placebo-controlled maintenance trial would be difficult. Schizophrenia is not as common in children and adolescents as it is in adults. The onset of schizophrenia prior to 13 years of age is rare, with a prevalence estimated at 1 in 10,000 patients. The estimated prevalence in adolescents (ages 13 through 17 years) is about 0.5%. Compliance problems that make a depot formulation attractive in adults are less common in the pediatric population because medication is generally administered by a parent, guardian, or caregiver. Relapse and hospitalization rates are very low (under 10%) in children and adolescents with schizophrenia. Clinical practice guidelines for the treatment of schizophrenia in children and adolescents recommend the use of oral antipsychotics, with only limited use of depot preparations.

Recommendations:

- No additional recommendations

The PeRC agreed with the Division to grant a full waiver for this product.

The pediatric page is attached for Abilify Maintena (aripiprazole extended-release suspension for injection).



1_Pediatric_Record
.pdf (59 KB)...

Thanks,

Courtney M. Suggs, Pharm.D., MPH

LCDR, USPHS
Regulatory Project Manager
Pediatric and Maternal Health Staff
Office of New Drugs, Immediate Office
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Ave.
Bldg 22, Room 6471
Silver Spring, MD 20993
Phone: (301) 796-2096
Email: courtney.suggs@fda.hhs.gov

Saini, Sonny

From: Saini, Sonny
Sent: Tuesday, April 24, 2012 2:46 PM
To: 'Goldberger, David'
Cc: Saini, Sonny
Subject: N 202,971 Microbiology comments

David,

We have the following Microbiology comments:

1. As mentioned previously, we are concerned about the lack of biological efficacy data for the sterilization validation studies (b) (4). Please provide the following information. (b) (4)

[Redacted content]

2. Provide the results from three sterilization validation studies for equipment and components used in the manufacture of the sterile drug substance at the Second Tokushima Factory. Provide these data for each (b) (4) of the biological indicators used.
3. Provide a summary of the results from the isolator decontamination validation studies in support of the sterile drug substance manufacture at the Second Tokushima Factory.
4. Provide the decontamination cycle parameters and validation studies for the isolator used for manufacture of the drug product at the (b) (4).
5. Provide the media and incubation conditions for the drug product environmental monitoring program at the (b) (4).

Regards,

Sonny

Sonny Saini, Pharm.D., MBA
CDR, USPHS

Senior Regulatory Project Manager
FDA/CDER/OND/ODE1/DPP
Phone: 301-796-0532
sonny.saini@fda.hhs.gov

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/s/

SANDEEP S SAINI
04/24/2012

Saini, Sonny

From: Saini, Sonny
Sent: Thursday, April 19, 2012 1:39 PM
To: 'Goldberger, David'
Cc: Bautista, Marji; Saini, Sonny; 'Elizaida.galarza@otsuka-us.com'
Subject: N 202,971 Request for additional analyses

Hi David,

Regarding N 202,971 study 31-07-246, please provide the results of the following analyses to assist us in the efficacy review of this trial.

1) For all subjects who were taking a 30 mg/day dose of oral aripiprazole at the end of Phase 2 (Oral Stabilization), entered Phase 3 (IM Depot Stabilization), and have PANSS scores at the final Phase 2 visit and week 2 and week 4 visits of Phase 3, please provide the PANSS total score mean, maximum/minimum, and standard deviation as well as the number of patients on which these calculations were based at each of these three time points. Also, kindly provide these statistics at the last Phase 2 assessment and the last available Phase 3 assessment for subjects who were taking a 30 mg/day dose of aripiprazole at the end of Phase 2, entered Phase 3, and dropped out prior to the week 4 assessment in Phase 3.

2) Please repeat the above analyses for all subjects taking an oral aripiprazole dose less than 30 mg/day at the end of Phase 2.

Regards,

Sonny

Sonny Saini, Pharm.D., MBA
 CDR, USPHS
 Senior Regulatory Project Manager
 FDA/CDER/OND/ODE1/DPP
 Phone: 301-796-0532
sonny.saini@fda.hhs.gov

From: Goldberger, David [<mailto:David.Goldberger@otsuka-us.com>]
Sent: Thursday, April 12, 2012 12:06 PM
To: Saini, Sonny; Chang, ShinYe; Toure, Juliette T; Patel, Hiren; Bender, William; Bouie, Teshara
Cc: Bautista, Marji; Galarza; Elizaida; Robert.Ashworth@otsuka-us.com
Subject: David Goldberger - Week of April 16

Dear FDA Colleagues,

I will be out of the office the Week of April 16. As I have secure ID and email with you I need to ask that you send any emails for me also to Marji Bautista Marji.bautista@otsuka-us.com and Liza Galarza Elizaida.galarza@otsuka-us.com. They both have secure ID and email will be able to open your message and

direct it to the correct people in my absence.

Thank you,
David

David Goldberger, RPh RAC
Senior Director Regulatory Affairs
Otsuka Pharmaceutical Development and Commercialization Inc.
1 University Square Drive, Suite 500
Princeton, NJ USA 08540
Phone: 1-609-524-6797
Mobile: 1-609-375-5479
Fax: 1-301-721-7290
Email: David.Goldberger@otsuka-us.com

Regulatory Affairs Executive Assistant: Marji Bautista
Phone: 240-683-3290/E-mail: marji.bautista@otsuka.com
Blackberry: 301-675-9882

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/s/

SANDEEP S SAINI
04/19/2012



NDA 202971

INFORMATION REQUEST

Otsuka Pharmaceutical Co., Ltd.
Attention: David Goldberger, R.Ph., RAC
Sr. Director, Regulatory Affairs
1 University Square Drive, Suite 500
Princeton, NJ 08540

Dear Mr. Goldberger:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aripiprazole Extended release suspension for injection.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Provide details of the drug substance (b) (4) identification methods including their acceptance criteria and validation. Clarify what levels of each of the other polymorphs will be acceptable under the proposed acceptance criteria for each test.
2. We recognize your justification for the lack of drug substance Heavy Metals and Residue on Ignition tests. However, these tests are standard quality tests and required under USP. These tests control general metals and other inorganic contaminants derived from (b) (4). Include these tests in the drug substance specification.
3. We recommend that the drug product specification be amended to include a separate identification test and acceptance criterion for the monohydrate polymorphic form due to the critical nature of this test to product performance and patient safety.
4. Revise the dissolution acceptance criteria to (b) (4) % at 15 minutes, (b) (4) % at 2 hours, and NLT (b) (4) % at 8 hours.
5. Justify with data whether (b) (4) can effectively remove the API particles (particularly submicron particles) in the dissolution samples for UV measurement. If not, provide supporting data demonstrating that the presence of API particles do not interfere and alter the UV measurement results.
6. We recommend the following modifications to the particle size acceptance criteria:

- (a) Lots manufactured with mean particle size at the lower end of the proposed acceptance range (b) (4) would be expected to have a pharmacokinetic profile similar to lot 090512-01 with a mean particle size of (b) (4). In vivo rat studies demonstrated that the latter had significantly different pharmacokinetic parameters compared to the lots used in clinical studies (b) (4). Therefore, we recommend increasing the lower end of the acceptance range for mean particle size to a size closer to a value that is expected to provide pharmacokinetic parameters similar to the clinical batch.
- (b) For similar reasons as given above, we recommend lowering of the upper range of the mean particle size distribution to a level more in line with that justified by the rat pharmacokinetic studies (b) (4).
- (c) We recommend lowering the (b) (4) acceptance criterion from (b) (4) to a level closer to the (b) (4) range where there is manufacturing/clinical experience.
7. The proposed label provides directions for the formulation of a 200 mg dose. Provide data demonstrating that this dosage strength can be reliably and accurately achieved.
8. Provide the instructions used by clinical personnel for the reconstitution of the clinical drug product lots, including the 300 mg strength dose. Provide evidence of the accuracy and reproducibility of these doses.
9. Provide an explanation for the (b) (4) peaks in Figure 3.2.P.2.1.1-11. Provide an explanation for the differences in the (b) (4) (Figure 3.2.P.2.1.1-11) and (b) (4) material (Figure 3.2.P.2.1.1-10).
10. Provide three sample drug product kits.
11. We recommend that the established name be “(aripiprazole) for extended release injectable suspension”.
12. Confirm that this product will be commercialized as a kit only.

If you have any questions, contact Teshara G. Bouie, Regulatory Project Manager, at (301) 796-1649.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

RAMESH K SOOD
03/30/2012

Saini, Sonny

From: Saini, Sonny
Sent: Tuesday, February 21, 2012 1:52 PM
To: 'Goldberger, David'
Cc: Saini, Sonny
Subject: Information Request for N 202,971

Hello David,

We have the following Microbiology comments/requests regarding your NDA 202,971 aripiprazole extended release suspension for injection that was submitted on September 26, 2011

Provide the following information or a reference to its location.

Convenience Kit

1. Confirm that all 510K devices included in the convenience package were approved as apyrogenic, sterile devices by CDRH. A representative certificate of analysis for each device component which indicates adequate sterility and endotoxin information would be adequate. Alternately, provide complete sterilization (b) (4) information on each device in the convenience kit.

Sterile Drug Substance

1. Confirm that no more than 3 batches of sterile drug substance will be manufactured in a campaign.
2. Indicate how, and at what location, the (b) (4) validation studies were sterilized.
3. Define the solution used for the post-use (b) (4) during production. The established minimum (b) (4) should be supported by data presented in Module 3.2.S.2.5 Appendix B, sponsor Table 6 in document ASL200907RE.
4. Module 3.2.S.2.5 Appendix B, sponsor Table 6 in document ASL200907RE states that the maximum contact time for the challenge studies was (b) (4). The proposed maximum contact time for production is (b) (4). Confirm that the data in Table 6 is an error or provide a justification for the submitted validation studies.
5. Also in reference to Module 3.2.S.2.5 Appendix B sponsor Table 6 in document ASL200907RE, provide additional information on footnote 22 which states "It confirmed that (b) (4) on appendix photograph were not test organisms by observation." No photographs were included in the submission and it is unclear how growth (b) (4) was determined to be an acceptable test result during these sterilization validation studies. We note that (b) (4) conditioning studies were conducted at a separate location from challenge studies.
6. Provide additional information on the transfer of sterile product from the (b) (4)
(b) (4)
7. Provide a description of the media and incubation conditions for detection of viable organisms in the environmental monitoring program.
8. Provide the parameters used for decontamination of the isolator for routine production and during validation studies.
9. Provide data to support the adequacy of nutrient growth medium to be used for environmental monitoring after inclusion in the isolator decontamination cycles.
10. Provide the name of the contract manufacturer used to (b) (4). Provide a summary of the validation studies which include a description of the validated loading pattern or maximum load, as applicable.
11. Provide additional information on the (b) (4) processing simulations.
 - a. Provide the acceptance criteria.

- b. Describe how (b) (4).
 - c. Provide a justification for not packaging all (b) (4).
 - d. Provide additional clarification on what happens to the excess (b) (4) that does not get packaged as part of the simulation.
 - e. Provide the results from growth promotion testing conducted on media-filled units.
 - f. Indicate the frequency of (b) (4) processing simulations.
12. Indicate how much drug substance is packaged into each bag.
 13. Provide a more detailed summary of the sterility test. In the summary please provide the solvent, the volume of media used and confirm that the sample size for the sterility test is (b) (4) containers.
 14. Explain the growth promotion test results from Table 3.2.S.2.5.8-1. Indicate why the growth promotion test results were negative for both test controls.
 15. Provide a more detailed summary of the endotoxin test method. Indicate what the limit of detection (lowest dilution) for the assay is.
 16. Provide the supplier for the (b) (4) used for drug substance packaging at Otsuka.

Drug Product

1. Describe the (b) (4).
2. Provide a justification for placing (b) (4).
3. Describe the (b) (4) steps used to add the sterile drug substance to the sterile vehicle solution. Indicate the level of personnel involvement and provide a description of how sterility is maintained.
4. Define (b) (4). Provide a comparison of the viscosity and osmolarity as compared to the vehicle.
5. The failure to include biological indicators to verify the adequacy of the sterilization (b) (4) is a concern. Provide additional information on what attempts have been made to include a biological indicator or what other sterilization methods have been investigated which might allow for inclusion of a biological indicator.

Please confirm receipt. You can contact me with any questions.

Regards,

Sonny

Sonny Saini, Pharm.D., MBA
 CDR, USPHS
 Senior Regulatory Project Manager
 FDA/CDER/OND/ODE1/DPP
 Phone: 301-796-0532
 sonny.saini@fda.hhs.gov

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/s/

SANDEEP S SAINI
02/21/2012



NDA 202971

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

Otsuka Pharmaceutical Co., Ltd.

c/o:

Otsuka Pharmaceutical Development and Commercialization, Inc.

1 University Square Drive, Suite 500

Princeton, NJ 08540

Attention: David Goldberger, R.Ph., RAC
Sr. Director, Regulatory Affairs

Dear Mr. Goldberger:

Please refer to your New Drug Application (NDA) dated and received September 26 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aripiprazole Extended release suspension for injection, 300mg or 400mg per vial.

We also refer to your October 14, 2011, submission, received October 17, 2011, requesting review of your proposed proprietary name, Abilify (b) (4). We have completed our review of the proposed proprietary name, Abilify (b) (4) and have concluded that this name is unacceptable for the following reasons:

The proposed proprietary name "Abilify (b) (4)" broadens the indication of the drug. (b) (4) "easily evokes the word (b) (4)" and is defined as (b) (4)

(<http://unabridged.merriam-webster.com/cgi-bin/unabridged>; accessed 10/25/11). The proposed product is indicated for the maintenance treatment of schizophrenia (relapse prevention). Schizophrenia is a psychotic disorder "characterized by disturbance in thinking involving a distortion of the usual logical relations between ideas, a separation between the intellect and the emotions so that the patient's feelings or their manifestations seem inappropriate to his life situation, and a reduced tolerance for the stress of interpersonal relations" (<http://unabridged.merriam-webster.com/cgi-bin/unabridged>; accessed 10/25/11). The proposed proprietary name suggests that the drug can be used to (b) (4)

Please note that the Federal Food Drug and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made, whether through

a proposed proprietary name or otherwise; this includes suggestions that a drug is better, more effective, useful in a broader range of conditions or patients, safer, has fewer, or lower incidence of, or less serious side effects or contraindications than has been demonstrated by substantial evidence or substantial clinical experience. [21 U.S.C. 321(n); see also 21 U.S.C. 352(a) & (n); 21 CFR 202.1(e)(5)(i);(e)(6)(i)].

We note that you have proposed an alternate proprietary name in your submission dated October 14, 2011. In order to initiate the review of the alternate proprietary name, Abilify Maintena, submit a new complete request for proprietary name review (See the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”). The review of this alternate name will not be initiated until the new submission is received.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sandra Griffith, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2445. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Sandeep Saini at (301) 796-0532.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
12/23/2011

Saini, Sonny

From: Saini, Sonny
Sent: Friday, December 02, 2011 9:42 AM
To: 'Goldberger, David'
Cc: Saini, Sonny
Subject: NDA 202,971 statistics request

Hello David,

Pleaser refer to Trial 31-07-246 in your submission of NDA 202971. The statistical reviewer could not duplicate the primary efficacy analysis results, since the original data sets (for example, PANSS and ENTCRIP) were not available. To facilitate the review process, please specify the order and dependencies in which these data were derived. For instance, if the subjects disposition listed in Table IAT-2.1 was generated by the SAS program EOS2.SAS, which uses the datasets EVALGRP0 and DOSE0 as inputs, we would like to know the sequence of the datasets that were used to derive these inputs, say:

Derived dataset	Created using input datasets:
EVALGRP0	DOSE0, CGI0, PANSS0, CGISS0
PANSS0	PANSS*, DOSE0
DOSE0	ENTCRIP*
CGI0	CGI I*, CGI S*, DOSE0, EFF0
EFF0	RELAPSE0, DOSE0
RELAPSE0	RELAPSE*, AE*, PANSS0, CGI0, CGISS0, RUF0, DOSE0
etc.
...	...

* non-derived datasets

Also, please provide all non-derived datasets, required for the analysis, i.e., those that should be listed in the column 2 but not in the column 1 of the example presented above.

Additionally, please provide the exact definition of the interim analysis dataset (whether it is based on the site numbers, date of randomization, subject randomization number, etc.) including an additional variable indicating which patients were included in the interim analysis, so we could perform the validation of the analysis independently.

Regards,

Sonny

Sonny Saini, Pharm.D., MBA
CDR, USPHS
Senior Regulatory Project Manager
FDA/CDER/OND/ODE1/DPP
Phone: 301-796-0532
sonny.saini@fda.hhs.gov

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/s/

SANDEEP S SAINI
12/02/2011

Saini, Sonny

From: Saini, Sonny
Sent: Thursday, December 01, 2011 10:53 AM
To: 'Goldberger, David'
Cc: Saini, Sonny
Subject: NDA 202,971 Response to your clarification questions

Follow Up Flag: Follow up
Flag Status: Red

Attachments: 202971 ClinPharm Questions_FINAL_OCP response.pdf



202971 ClinPharm
Questions_FIN...

Hello David,

Please see the attachment for our responses to your clarification questions for N 202,971.
Please submit the data we requested by 12/14/11.

Regards,

Sonny

Sonny Saini, Pharm.D., MBA
CDR, USPHS
Senior Regulatory Project Manager
FDA/CDER/OND/ODE1/DPP
Phone: 301-796-0532
sonny.saini@fda.hhs.gov

1 Clinical Pharmacology

Request for clarification to the Clinical Pharmacology questions and potential review issues are provided below:

1.1 Question 1

1.1.1 Question

In clinical practice, patients might not be able to receive the aripiprazole ER suspension injection exactly following the scheduled time. Therefore you are asked to conduct (e.g., if the dose were to be given 2 days prior to and 2 days after the scheduled dosing time)

1.1.2 Background information

We have performed simulations where administration of aripiprazole IM depot was delayed or missed. The simulations included situations where delays of varying duration in the timing of the 2nd, 3rd, 4th and 10th (representing steady-state) aripiprazole IM depot administrations occurred (see Summary of Clinical Pharmacology Section 2.7.2.4.1.3.5). The simulations included the following scenarios:

- Delay of 7 days for the 2nd and 3rd aripiprazole IM injections,
- Delay of 14 days for the 4th and 10th (representing steady-state) aripiprazole IM depot injections,
- Delay of longer than 7 days (i.e. 8 days) for the 2nd and 3rd with concomitant oral aripiprazole administration for 14 days
- Delay of longer than 14 days (i.e. 15 days) for the 4th and 10th (representing steady-state) aripiprazole IM depot injections with concomitant oral aripiprazole administration for 14 days

1.1.3 Clarification

The simulations provided in the NDA and the proposed labeling include scenarios of “flexible dosing schedule” up to 7 days for 2nd and 3rd aripiprazole IM depot administrations and up to 14 day for 4th and 10th IM depot administrations. We are requesting further clarification if additional simulations should cover individual days up to 7 and 14 days for the 2nd and 3rd and 4th and 10th IM depot administrations, respectively? Additionally, as we have not conducted simulations where aripiprazole IM depot is administered earlier than 28 days, further clarification is requested on the

simulations, i.e. how many days of advance administration should be included in the simulations?

FDA Response:

Thank you for explaining and summarizing the simulations performed. Upon reevaluation of the information already provided, no additional simulations are necessary.

1.2 Question 2

1.2.1 Question

*Please submit the datasets and codes/scripts for reviewers to recreate all the simulations described in Table S8-20 entitled “Description of Population and Dosing and Location of Corresponding Graphs and Statistics for Each Simulation Scenario Evaluated” from page 101 of Report 31-11-287 (Pop PK M&S Report). All model codes or control streams, output listings and scripts used to generate plots should be provided for all simulations performed. Files should be submitted as ASCII text files with *.txt extension (e.g., myfile_ctl.txt, myfile_out.txt)*

1.2.2 Background information

Each simulation scenario involved the following inputs and outputs:

- NONMEM input data file(s)
- Control stream(s) for simulation
- NONMEM table file(s)
- SAS program to process the NONMEM output file(s) and output a SAS dataset(s)
- SAS program used to generate the graph of the scenario

1.2.3 Clarification

We wish to clarify the following:

- Does the reviewer intend ‘script’ to include only the NONMEM codes and outputs or should the SAS programs to process data and the SAS programs that generate the plots also be included?

- Does the reviewer intend the output listings to include only the NONMEM table files(s) or should the processed output (SAS dataset(s)) also be included?
- If SAS dataset(s) should be included, should they be sent in transport format (.xpt) instead of ASCII format?

Of note, if the answers to all of the above questions are affirmative, then the estimated total size of the files is approximately 8 GB. In that case we wish to provide the data in the form of electronic mass storage devices. Please also confirm the proper media for transfer of such information.

FDA Response:

SAS programs to process the data and generate plots should be included, in addition to the NONMEM codes. For the output listings, just the NONMEM table file will suffice. There is no need to submit the processed SAS output (i.e., SAS datasets).

In addition, a brief outline of the work flow should be included so that the reviewer can reproduce simulation results.

As to the media for transfer of data, a mass storage device (e.g., CD) is acceptable.

1.3 Question 3

1.3.1 Question

With regard to the CYP2D6 pharmacogenetic analyses, please submit a dataset (in SAS .xpt format) containing individual CYP2D6 genotypes and subject identifiers that link the population PK and core trial datasets. Also, please submit a summary of the genotyping methods, tested alleles, quality control procedures, and phenotype parameterization.

1.3.2 Clarification

No clarification is needed.

1.4 Question 4

1.4.1 Question

Please submit individual aripiprazole and dehydro-aripiprazole plasma concentration data for both studies CN138020 and 31-05-244 in SAS.xpt format.

1.4.2 Background information

The Individual aripiprazole plasma concentration data used for the development of the Population PK model are in the population pharmacokinetic dataset located in the NDA; however the dataset did not include dehydro-aripiprazole concentrations for the mentioned studies.

1.4.3 Clarification

Please confirm if the dataset (in SAS.xpt format) including individual aripiprazole and dehydro-aripiprazole concentrations with columns specifying the following variables would be sufficient?

- Protocol number
- Analyte (aripiprazole, dehydro-aripiprazole)
- Subject ID
- Scheduled PK time
- Actual PK time

FDA Response:

Additional columns, such as concentration of each analyte, dose of aripiprazole, and formulation of aripiprazole (Immediate-Release IM or IM Depot) should be included in the dataset.

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/s/

SANDEEP S SAINI
12/01/2011



NDA 202971

FILING COMMUNICATION

Otsuka Pharmaceutical Development & Commercialization, Inc.
Attention: David Goldberger, R.Ph., RAC
Senior Director, Regulatory Affairs
2440 Research Blvd.
Rockville, MD 20850

Dear Mr. Golberger:

Please refer to your New Drug Application (NDA) dated and received on September 26, 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Abilify (b) (4) (aripiprazole) extended release suspension for injection 300 mg/vial and 400 mg/vial.

We also refer to your amendments dated November 7, 2011 and November 9, 2011.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is July 26, 2012.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by July 5, 2012.

During our filing review of your application, we identified the following potential review issues and have the following requests:

Clinical Pharmacology

1. In clinical practice, patients might not be able to receive the aripiprazole ER suspension injection exactly following the scheduled time. Therefore you are asked to conduct

simulations exploring flexible dosing windows for the initial dose and maintenance dose (e.g., if the dose were to be given 2 days prior to and 2 days after the scheduled dosing time).

2. Please submit the datasets and codes/scripts for reviewers to recreate all the *simulations* described in Table S8-20 entitled “Description of Population and Dosing and Location of Corresponding Graphs and Statistics for Each Simulation Scenario Evaluated” from page 101 of Report 31-11-287 (Pop PK M&S Report).

All model codes or control streams, output listings and scripts used to generate plots should be provided for all simulations performed. Files should be submitted as ASCII text files with *.txt extension (e.g., myfile_ctl.txt, myfile_out.txt)

3. With regard to the CYP2D6 pharmacogenetic analyses, please submit a dataset (in SAS .xpt format) containing individual CYP2D6 genotypes and subject identifiers that link the population PK and core trial datasets. Also, please submit a summary of the genotyping methods, tested alleles, quality control procedures, and phenotype parameterization.
4. Please submit individual aripiprazole and dehydro-aripiprazole plasma concentration data for both studies CN138020 and 31-05-244 in SAS .xpt format.

Product Quality Microbiology

5. Submit the protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product (b) (4)

Processing Guidance which can be found at the following location:
[http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ \(b\) \(4\) .pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ (b) (4) .pdf).

6. The storage of reconstituted drug product should be not more than 4 hours at room temperature or not more than 24 hours under refrigeration. Please revise the label or provide studies which demonstrate that low levels of inoculated microorganisms will not proliferate under the labeled storage conditions. The report should describe test methods and results that employ a minimum countable inoculum to simulate potential microbial contamination that may occur during product constitution. It is generally accepted that growth is evident when the population increases more than 0.5 Log₁₀. The test should be run at the label's recommended storage conditions and be conducted for 2 to 3-times the label's recommended storage period and using the label-recommended fluids. Periodic intermediate sample times are recommended. Challenge organisms may include strains described in USP <51> plus typical skin flora or species associated with hospital-borne infections. In lieu of these data, the product labeling should recommend that the post-constitution storage period is not more than 4 hours at room temperature.

Center for Devices and Radiological Health (CDRH)

7. CDRH has concerns regarding the Smiths Medical needle this is included in the aripiprazole administration kit. It is unlikely that these issues can be adequately addressed solely by your proposed pharmacovigilance plan. CDRH will contact the 510(k) holder Smiths Medical regarding the additional performance data that is required for this device.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

Highlights (HL) –

- 1) Patient Counseling Information Statement

Must include the verbatim statement: “**See 17 for Patient Counseling Information and Medication Guide**”.

Full Prescribing Information (FPI) -

- 2) A horizontal line must separate the Table of Contents and FPI.
- 3) **Adverse Reactions Section** - Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided.
- 4) **Adverse Reactions Section** - For the “Clinical Trials Experience” subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions: “Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

We request that you resubmit labeling that addresses these issues by December 23, 2011. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

Pediatric Research Equity Act

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, contact Sonny Saini, Pharm.D., MBA, Senior Regulatory Project Manager, at sonny.saini@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

MITCHELL V Mathis
11/21/2011
For Dr. Laughren



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202971

ADVICE LETTER

Otsuka Pharmaceutical Company, Ltd.
c/o Otsuka Pharmaceutical Development & Commercialization, Inc.
Attention: David Goldberger, R.Ph., RAC
Senior Director, Regulatory Affairs
2440 Research Blvd.
Rockville, MD 20850

Dear Mr. Goldberger:

Please refer to your New Drug Application (NDA) dated and received September 26, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ABILIFY MAINTENA (aripiprazole) extended-release injectable suspension for intramuscular (IM) injection 300 mg/vial and 400 mg/vial.

Reference is also made to your submission dated August 31, 2012, which constituted a complete response to our action letter dated July 26, 2012.

The Agency would like to inform you that during a recent inspection of the [REDACTED] (b) (4) [REDACTED] manufacturing facility, which is the sterile water supplier for this application, our field investigator conveyed deficiencies to the representative of the facility.

Satisfactory resolution of these deficiencies is required before this application may be approved.

If you have any questions, contact Sonny Saini, Pharm.D., MBA, Regulatory Project Manager, at sonny.saini@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

THOMAS P LAUGHREN
11/13/2012



NDA 202,971

NDA ACKNOWLEDGMENT

Otsuka Pharmaceutical Company, Ltd.
c/o Otsuka Pharmaceutical Development & Commercialization, Inc.
Attention: David Goldberger, R.Ph., RAC
Senior Director, Regulatory Affairs
2440 Research Blvd.
Rockville, MD 20850

Dear Mr. Goldberger:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Aripiprazole (OPC-14597) extended release suspension for injection
300 mg/vial and 400 mg/vial

Date of Application: September 26, 2011

Date of Receipt: September 26, 2011

Our Reference Number: NDA 202,971

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 24, 2011 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Psychiatry Products

5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size.

Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>

If you have any questions, call me at (301) 796-0532.

Sincerely,

{See appended electronic signature page}

Sonny Saini, Pharm.D., MBA
CDR, USPHS
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

SANDEEP S SAINI
10/04/2011



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 67,380

MEETING MINUTES

Otsuka Pharmaceutical Company, Ltd.
c/o Otsuka Pharmaceutical Development & Commercialization, Inc.
Attention: David Goldberger, R.Ph., RAC
Senior Director, Regulatory Affairs
1 University Square Drive, Suite 500
Princeton, NJ 08540

Dear Mr. Goldberger:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for aripiprazole Intramuscular Depot Formulation.

We also refer to the meeting between representatives of your firm and the FDA on June 7, 2011. The purpose of the meeting was to discuss the nonclinical and clinical development program results and receive FDA feedback on the proposed NDA for aripiprazole intramuscular (IM) depot (OPC-14597) for the maintenance treatment of schizophrenia.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call CDR Sonny Saini at (301) 796-0532.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA
Meeting Date and Time: June 7, 2011; 1:00 – 1:30 p.m.
Meeting Location: WO 22 Room 1415
Application Number: IND 67,380
Product Name: Aripiprazole
Indication: Schizophrenia
Sponsor/Applicant Name: Otsuka Pharmaceutical Company, Ltd.
Meeting Chair: Thomas Laughren, M.D.
Meeting Recorder: Sonny Saini, Pharm.D., MBA

FDA Participants:

Thomas Laughren, M.D., Division Director, Division of Psychiatry Products
Mitchell Mathis, M.D., Deputy Division Director
Jing Zhang, M.D., Clinical Team Leader
Greg Dubitsky, M.D., Clinical Reviewer
Maju Mathews, M.D., Clinical Reviewer
Aisar Atrakchi, Ph.D., Pharmacology/Toxicology Team Leader
Sonia Tabacova, Ph.D., Pharmacology/Toxicology Reviewer
Andrejus Parfionovas, Ph.D., Statistical Reviewer
Jogarao Gobburu, Ph.D., OCP Team Leader
Huixia Zhang, Ph.D., OCP Reviewer
Peiling Yang, Ph.D., Statistician Team Leader
David Claffey, Ph.D., Chemist, ONDQA
Kellie Taylor, Pharm.D., Associate Director, OSE/DMEPA
Sonny Saini, Pharm.D., MBA, Project Manager

Otsuka Pharmaceuticals Participants:

Judith Atkins PhD, Manager, Regulatory Affairs
Khaled Bannout MD, Associate Director, Clinical Safety & Pharmacovigilance
William Carson MD, President and CEO
David Goldberger RPh, MS, Senior Director, Regulatory Affairs
Na Jin MS, Manager, Biostatistics
Robert McQuade PhD, Senior Vice President, Global Medical & Regulatory Affairs
Pam Perry MS, Associate Director Global Clinical Development
Ray Sanchez MD, Vice President, CNS Global Clinical Development
Haruhiko Sugino PhD, Global Product Coordinator

Background:

Regulatory History

Aripiprazole is a second generation antipsychotic, currently available in tablet (NDA 21-436), oral solution (NDA 21-713), orally disintegrating tablet (NDA 21-729), and injectable formulation (NDA 21-866). Aripiprazole has been widely used since its initial approval in 2002 for the treatment of schizophrenia. The current approved indications for oral formulations of aripiprazole include: treatment of schizophrenia; acute treatment of manic or mixed episodes associated with bipolar I disorder as monotherapy and as an adjunct to lithium or valproate; maintenance treatment of bipolar I disorder, both as monotherapy and as an adjunct to lithium or valproate; adjunctive treatment of major depressive disorder; and treatment of irritability associated with autistic disorder. The current approved indication for injectable formulation of aripiprazole is acute treatment of agitation associated with schizophrenia or bipolar I disorder.

On March 4, 2003, the Division held a pre-IND meeting with representatives from Otsuka Pharmaceuticals and Bristol Myers Squibb to discuss their proposed development program for an IM depot formulation of aripiprazole. During that meeting, we indicated that non-inferiority trials, as proposed by the sponsor, would not be acceptable to provide primary evidence of efficacy. We recommended three alternatives: 1) a trial that included an ersatz placebo control, 2) a trial to show superiority over an active control, or 3) a relapse prevention trial to demonstrate a maintenance effect. IND 67,380 was submitted on May 12, 2003, to provide for the conduct of studies to support a future NDA for aripiprazole IM depot in the maintenance treatment of schizophrenia.

Aripiprazole IM Depot Development Program

Currently, the development program consists of eight studies:

Phase 1 Clinical Pharmacology Trials

- CN138-020 - in vivo release characteristics of single dose aripiprazole IM depot (15, 50, 100, 200, 300, and 400mg).
- 31-07-002 - single dose PK and tolerability (100, 200, 300, and 400mg).
- 31-05-244 - multiple dose PK & tolerability (200, 300, and 400mg q4 weeks for 5 months).

These three trials were conducted in patients with schizophrenia or schizoaffective disorder and all are complete.

Controlled Phase 3 Trials

- 31-07-246 - stabilization of schizophrenic patients on aripiprazole IM depot for 12 weeks followed by 2:1 randomization to aripiprazole IM depot (300 or 400mg q4 weeks) or IM depot placebo for 52 weeks. This is the pivotal efficacy study for the NDA.
- 31-07-247 - stabilization of schizophrenic patients on oral aripiprazole followed by 2:2:1 randomization to 38 weeks of aripiprazole IM depot 300 or 400mg q4 weeks, aripiprazole IM depot 50 or 25mg q4 weeks, or oral aripiprazole (10-20 mg/day) to demonstrate non-inferiority of IM depot versus oral aripiprazole as maintenance treatment.
- 31-08-003 - stabilization of schizophrenic patients on oral aripiprazole followed by 1:1 randomization to 26 weeks of aripiprazole IM depot (300 or 400mg q4 weeks) or oral

aripiprazole (6-24 mg/day) to demonstrate non-inferiority of IM depot versus oral aripiprazole as maintenance treatment.

Trial 31-07-246 is complete. The other two trials are ongoing and data will remain blinded at the time of the NDA submission.

Open-label uncontrolled trials

- 31-08-248 - 52 week open-label study enrolling *de novo* patients and rollover patients from 31-07-246 or 31-07-247.

- 31-10-270 - open-label extension study for patients who completed 31-08-248.

Both studies are ongoing.

An additional Phase 1 trial in Japan (31-10-002) is planned for mid-2011. It is expected that data from this study will be available for inclusion in the 120-Day Safety Update.

Dose Selection

Pharmacokinetic simulations indicated that therapeutic plasma concentrations of aripiprazole may be produced by a dosing regimen of 10 mg/day oral aripiprazole for the initial two weeks of treatment with either 200, 300, or 400mg aripiprazole IM depot every 28 days. These findings were evaluated *in vivo* in trial 31-05-244. Results showed that 400mg IM depot dosing resulted in mean aripiprazole trough concentrations equal to or greater than oral dosing of 10 mg/day. The 300mg IM depot dose produced concentrations somewhat lower than with aripiprazole 10 mg/day oral dose. Following 200mg IM depot dosing, mean concentrations were consistently below the trough concentrations with 10 mg/day oral dosing. Thus, the 400mg IM depot dose was chosen as the starting dose for pivotal Phase 3 trials, with a dose decrease to 300mg if 400mg was not tolerated. Also, subjects would receive oral aripiprazole (10 to 20 mg/day) for the initial two weeks of IM depot dosing to maintain therapeutic aripiprazole concentrations after starting IM depot dosing.

Exposure

The NDA safety database will encompass 980 subjects who have received multiple doses of aripiprazole IM depot. In studies 31-07-246 and 31-08-248 together, 350 subjects have received ≥ 7 consecutive injections (or ≥ 6 months of exposure) while 123 subjects have received ≥ 13 consecutive injections (or ≥ 12 months of exposure). At the time of the 120-Day Safety Update to the NDA, it is estimated that an additional 300 subjects will have been exposed for ≥ 6 months and an additional 200 subjects will have been exposed for at least one year.

NDA Submission Contents

The NDA submission will contain complete study reports for trials 31-07-246, 31-05-244, and 31-07-002; abbreviated study reports for trials 31-08-248 and 31-10-270; and synopses for trials CN138-020, 31-07-247, and 31-08-003.

The proposed Integrated Summary of Safety (ISS) will organize trials into the following four pools for data analysis:

- All Multiple Dose Trials
31-07-246 (SB and DB phases)

- 31-08-248
- 31-10-270
- 31-05-244
- Controlled Phase 3 Trial
 - 31-07-246 (DB phase)
- Uncontrolled Phase 3 Trials
 - 31-07-246 (SB phase)
 - 31-08-248
 - 31-10-270
- Single Dose Trials
 - CN138-020
 - 31-07-002

All study pools will include information on exposure, subject demographics and disposition, deaths, all serious adverse events, adverse events associated with discontinuation of therapy, all treatment-emergent adverse events, potentially clinical relevant (PCR) laboratory values, vital signs, ECG's; and Hy's law analyses. Safety data from study 31-07-246 will also include C-SSRS suicide analyses.

Since there is only one pivotal efficacy trial, an Integrated Summary of Efficacy will not be submitted.

Pivotal Efficacy Study (31-07-246)

The pivotal trial for the NDA submission will be 31-07-246. Over 1,400 adult patients with a DSM-IV-TR diagnosis of schizophrenia for at least three years and who required chronic treatment with an antipsychotic entered into the study. This study consisted of a screening phase of 2 to 42 days and four treatment phases (Phase 1 through 4).

Eligible subjects who received oral antipsychotic treatment other than aripiprazole prior to the study entered Phase 1 (oral conversion), during which they were cross-titrated from the other agent to oral aripiprazole over a period of four to six weeks with the goal of achieving a target dose of aripiprazole 10 to 15 mg/day no later than week 6. Patients successfully converted to oral aripiprazole entered Phase 2. Patients who were receiving oral aripiprazole prior to the study entered Phase 2 immediately after screening.

Phase 2 (oral stabilization) lasted a minimum of four weeks and a maximum of 12 weeks. Patients were assessed every two weeks and stabilized on oral aripiprazole 10 to 30 mg/day. Stability was defined as fulfillment of all of the following for four consecutive weeks:

- 1) outpatient status.
- 2) PANSS total score ≤ 80 .
- 3) PANSS score ≤ 4 on each of the following items:
 - conceptual disorganization.
 - suspiciousness.
 - hallucinatory behavior.
 - unusual thought content.

4) CGI severity score ≤ 4 .

5) CGI-SS ≤ 2 (mildly suicidal) on Part 1 and ≤ 5 (minimally worse) on Part 2.¹

Subjects who met stability criteria entered Phase 3 (IM depot stabilization) during which they received single-blind aripiprazole IM depot 400mg every four weeks and began a stabilization phase of up to 36 weeks, the length depending on how long it took to meet the above stability criteria for 12 consecutive weeks.² Oral aripiprazole dosing (10 to 20 mg/day depending on the Phase 2 dose and clinical need) was continued for the first two weeks of Phase 3 to maintain therapeutic plasma concentrations while the IM depot treatment reached steady state. A decrease in dose to 300mg every four weeks was permitted for tolerability as was a single return to the 400mg dose, if required. Subjects who met stability criteria for 12 consecutive weeks entered Phase 4.³

Phase 4 (randomized IM depot) was a randomized, double-blind, placebo-controlled, 52-week maintenance phase. Patients were randomized in a 2:1 ratio to either aripiprazole IM depot (300 or 400mg) or placebo IM injection every four weeks. The starting dose in Phase 4 was the final dose in Phase 3 but the dose in Phase 4 could be adjusted (one time down to 300mg and one time back up for patients starting at 400mg and one time up to 400mg and one time back down for patients starting at 300mg).

An unblinded Site Study Drug Manager, different from staff involved in performing study assessments, prepared and administered double-blind IM depot study medication due to a difference in the appearance of reconstituted aripiprazole compared to placebo (milky white suspension versus a clear solution).

Patients were monitored for signs of exacerbation or impending relapse during clinic visits every two weeks. In addition, patients were contacted by phone between visits to determine whether the scheduled visit should be moved forward. Exacerbation/ impending relapse was defined as meeting any of the following conditions:

- 1) CGI improvement score ≥ 5 (minimally worse) AND one of the following two criteria: a) an increase in any of the following PANSS item scores to a score >4 with an absolute increase ≥ 2 on that item since randomization: conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content OR b) an increase on any of these items to a score >4 and an absolute increase ≥ 4 on the combined score from these items since randomization.
- 2) hospitalization due to worsening of psychotic symptoms (including partial hospitalization) but excluding hospitalization for psychosocial reasons.

¹ The CGI-SS (Clinical Global Impression of Severity of Suicide) is comprised of two parts that assess the severity of suicidality over the prior week. Part 1 rates severity on a five point scale (1=not suicidal at all to 5=attempted suicide). Part 2 rates change from baseline in suicidality on a seven point scale (1=very much improved to 7=very much worse).

² All IM injections were into the gluteal muscle.

³ Subjects were allowed one excursion from the stability during the 12 week period as long as it did not occur on the final visit of Phase 3.

- 3) CGI-SS score of 4 (severely suicidal) or 5 (attempted suicide) on Part 1 and/or 6 (much worse) or 7 (very much worse) on Part 2.
- 4) violent behavior resulting in clinically significant self-injury, injury to another person, or property damage.

The appearance of relapse resulted in withdrawal from the study for lack of efficacy.

The primary efficacy endpoint was the time from randomization to exacerbation or impending relapse, as defined above, during Phase 4. The efficacy intent-to-treat sample consisted of all patients randomized to double-blind treatment. Statistical comparison was performed using the log-rank test to compare the aripiprazole treatment group versus placebo. Interim analyses were planned after approximately 50% and 75% of events were accrued.

The key secondary variable was the percentage of patients meeting impending relapse criteria at endpoint of the placebo-controlled phase. If the primary hypothesis was rejected at an alpha level of 0.05, then the key secondary endpoint was analyzed using the Chi Square test and tested at the 0.05 level.

The Data Monitoring Committee recommended early trial termination after the first pre-planned interim analysis based on significant efficacy results in favor of aripiprazole IM depot on the primary endpoint ($p < 0.0001$). The data cut-off for the interim analysis was June 8, 2010, and the trial was terminated on July 26, 2010. The final analysis included 403 randomized subjects and 80 events of impending relapse. Aripiprazole IM depot was superior to placebo in delaying impending relapse ($p \leq 0.0001$). On the key secondary endpoint, the percentage of patients meeting criteria for impending relapse was significantly lower in the aripiprazole IM depot group (10.0%) compared to the placebo group (39.6%) ($p < 0.0001$).

Pediatric Waiver Request

The sponsor requests a waiver of requirements for pediatric studies with aripiprazole IM depot based on the following considerations:

- schizophrenia is less common overall in children and adolescents compared to adults. The onset of schizophrenia prior to age 13 is rare, with a prevalence estimated at 1 in 10,000. The estimated prevalence in adolescents (ages 13 through 17 years) is about 0.5%.
- compliance problems that make a depot formulation attractive in adults are less common in the pediatric population because medication is generally administered by a parent, guardian, or caregiver. Relapse rates and hospitalization are very low in children and adolescents with schizophrenia.
- clinical practice guidelines for the treatment of schizophrenia in children and adolescents recommend the use of oral antipsychotics, with only limited use of depot preparations.
- children and adolescents are more averse to receiving intramuscular injections. Even one injection may lead to a negative perception of treatment and negatively affect future treatment with any antipsychotic.
- children and adolescents have a smaller gluteal muscle mass for injection of depot medication. This may lead to differences in absorption and distribution. Also, the smaller available surface area restricts injection site options, even with rotation of sites.

- recruiting pediatric patients for a placebo-controlled study may not be feasible because 1) this population is already well controlled with oral treatments so there is little incentive for a depot formulation and randomization to placebo may place patients at risk of relapse, 2) this population is inherently averse to receiving injections, and 3) ethical concerns may lead to difficulty obtaining IRB approval.

Risk Evaluation and Mitigation Strategy

The sponsor does not believe that there is any risk that would require a Risk Evaluation and Mitigation Strategy (REMS). It is felt that the following will be adequate to monitor the safety of aripiprazole IM depot treatment:

- an ongoing pharmacovigilance plan that includes systematic collection of adverse event information, real time and periodic assessment of single and aggregate safety reports to identify potential signals, and submission of aggregate reports as required by regulations.
- the sponsor recommends that the Medication Guide be distributed to outpatients at the time of first injection, upon request at subsequent injections, and after any material change to the document. There would be no requirement for distribution to inpatients, in accordance with draft guidance from the Agency.⁴ However, the Medication Guide would be distributed to any inpatient who requests it.

Non-clinical Background

The primary NDA for aripiprazole, NDA 21-436 (schizophrenia, oral tablet; submitted 31 October 2001), contained the majority of the nonclinical studies that were conducted to support the use of this drug as an oral formulation for schizophrenia. Supplemental NDAs (sNDAs) submitted to the FDA consisted of an oral solution formulation for schizophrenia (NDA 21-713, submitted 20 November 2003), an oral disintegrating tablet formulation for schizophrenia (NDA 21-729, submitted 22 December 2003) and an injectable formulation for schizophrenia and bipolar disorder (NDA 21-866, submitted 29 November 2005).

The pharmacology, including safety pharmacology, of aripiprazole has been thoroughly described in several approved NDAs. The details from the nonclinical studies will not be described in the current NDA as these are described in the NDAs referenced above. The pharmacology tabular summaries will not be included in this NDA.

The pharmacokinetics of aripiprazole have been adequately characterized in vivo in mice, rats, dogs, and monkeys, and in model test systems in vitro in a previously approved NDA (21-436). In the current NDA for the intramuscular (IM) depot formulation of aripiprazole, several additional PK studies have been conducted to support this program. The PK data showed that after injection of aripiprazole IM depot formulation in rats the C_{max} and AUC of aripiprazole increased with the dose increment, and there was no sex difference in the plasma concentrations. Aripiprazole injected as a depot formulation was stable at the injection site without being metabolized or decomposed. From the residual amount of aripiprazole in the injection site, it is

⁴ U.S. Food and Drug Administration. Draft Guidance for Industry: Medication Guides - Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS), February 2011.

presumed that the absorption of aripiprazole increased approximately from 39% up to 84% from 168 hours to 1008 hours post injection, indicating a controlled release of the drug into systemic circulation. The absolute bioavailability assessed in minipigs indicated that aripiprazole was completely bioavailable from IM and SC routes ($F = 111\%$ and 102% , respectively) and incompletely bioavailable after PO route ($F = 22.3\%$), which is suggestive of the extensive first pass metabolism and/or incomplete absorption of aripiprazole following PO administration.

Assessment of aripiprazole metabolites OPC-14857, DM-1451, DM-1452, OPC-3373 and 1-(2, 3 dichlorophenyl)piperazine (DCPP) following single IM injections of aripiprazole IM depot formulation to rats, showed that the plasma concentrations of DM-1451 increased nonlinearly with the dose increment while OPC-14857, DM-1452, OPC-3373 and DCPP were lower than the lower limit of quantification (LLQ). The rank order of the C_{max} and AUC_t for aripiprazole and its metabolites was aripiprazole > DM-1451 > OPC-3373 > OPC-14857.

The excretion of total radioactivity within 168 hours after single IM administration of ^{14}C -aripiprazole IM rapid formulation to rats accounted for 96.9% and 97.7%, in males and females, respectively, indicating that the excretion was almost complete.

Toxicology

The safety of aripiprazole was evaluated in single- and repeat-dose oral toxicity studies in rats and monkeys, a battery of in vitro and in vivo genotoxicity studies, carcinogenicity studies in mice and rats, oral reproductive and developmental studies in rats and rabbits, and juvenile toxicity studies in rats and dogs. In addition, studies were conducted with aripiprazole to characterize the local tolerance, dermal sensitization, phototoxicity, antigenicity, immunotoxicity, and physical dependence and abuse potential. The effects of aripiprazole on serum reproductive hormones were examined in mice and rats. Investigative studies were conducted to determine the basis for adrenocortical changes observed in toxicity studies and the retinal degeneration observed in rats. Additionally, some aripiprazole metabolites were tested for general and genetic toxicity because they were present as impurities and their levels exceeded the specified qualification threshold. Two metabolites of aripiprazole (OPC-14857, OPC-3373) found in animals and humans were tested in single-dose toxicity studies in rats and bacterial gene-mutation tests, and a metabolite (also a synthetic intermediate) of aripiprazole (2,3-DCPP) was tested in a repeat-dose toxicity study in rats and in genetic toxicity tests.

These toxicological studies have been described in several approved NDAs, primarily in NDA 21-436 (schizophrenia, oral tablet; submitted 31 October 2001) that contained the majority of the nonclinical studies that support the use of this drug as an oral formulation.

In the current NDA for the IM depot formulation of aripiprazole, several additional single- and repeat-dose toxicity studies and local tolerance studies have been conducted using the proposed formulation (as shown below).

Aripiprazole IM Depot: Completed Toxicity Studies

Single-Dose Toxicity: Dogs (2 studies)

Repeat-Dose Toxicity:

- Preliminary 4 wk and 26-wk toxicity studies in rats and dogs
- 52-wk study in dogs

- 2-wk and 4-wk studies in monkeys

Genotoxicity: The genotoxic potential of aripiprazole was assessed in support of the aripiprazole oral tablet formulation. Results of all genetic toxicity studies (in vitro and in vivo test systems) indicated that aripiprazole was not genotoxic.

The carcinogenic potential of aripiprazole was evaluated in mice and rats in support of the aripiprazole oral tablet formulation. Aripiprazole did not induce tumors in male mice or rats. In female mice, the incidences of pituitary gland adenomas and mammary gland adenocarcinomas and adenoacanthomas were increased; in female rats, the incidence of mammary gland fibroadenomas was also increased, likely related to prolactin increase. Additionally, increased incidences of adrenocortical carcinomas and combined adrenocortical adenomas/carcinomas were noted in female rats at daily oral doses exceeding the MTD and at an exposure 10 times that observed at the oral maximum recommended human dose of 30 mg.

Reproductive and Developmental Toxicity: The reproductive and developmental toxicity of aripiprazole was previously evaluated in rats and rabbits following oral or IV administration. Additional developmental and reproductive toxicity studies were not conducted with the IM depot formulation. A waiver for undertaking these studies was granted by the FDA (email communication from Keith Kiedrow, 23 June 2010).

Local Tolerance: Numerous local tolerance studies were conducted in rats, rabbits, dogs and monkeys with the IM depot formulation. Microscopically, the primary finding at the injection site from these studies was a localized, granulomatous inflammatory response to deposited drug consistent with a foreign-body reaction in response to deposited drug (polymorphic, (b) (4)). This inflammation was not completely resolved by termination of the studies.

Questions:

Clinical

1. Otsuka believes that the clinical trials to be presented in the NDA are sufficient to support the NDA filing and subsequent approval of aripiprazole IM depot for the maintenance treatment of schizophrenia.

The clinical development program for aripiprazole IM depot that is outlined in this pre-NDA briefing document is consistent with what was presented at the pre-IND meeting on 04 March 2003 and subsequent communications with the FDA.

Does the Division agree that the clinical trials to be presented in the NDA are sufficient to support the proposed indication for aripiprazole IM depot for the maintenance treatment of schizophrenia?

Preliminary Comments:

Yes, the clinical trials should be adequate to support the NDA submission. The filability and approvability of the application will, of course, be a matter for review.

Discussion at Meeting:

No further discussion.

2. The structure of the ISS is presented in Appendix 3.1.

Does the Division agree on the following?

- The organization and structure of the ISS
- The format and presentation of in-text tables in the ISS
- The list of Safety Topics of Special Interest

Preliminary Comments:

The heterogeneity of the trials in terms of study design and completion status is too great to permit a meaningful pooling of trials except to provide information on overall exposure in terms of duration and dose. The review of safety analyses will likely be performed for each study individually, with the primary focus on the pivotal trial 31-07-246.

The Safety Topics of Special Interest (EPS and EPS-related adverse events, effects on glucose, effects on lipids, weight, QTc intervals, effects on prolactin, injection site effects, WBC abnormalities, orthostasis, and suicidality) are acceptable.

The submission must include a demographic subgroup analysis of adverse event incidence for common, possibly drug-related events (i.e., those occurring in at least 5% of aripiprazole IM depot patients and at an incidence at least twice that of placebo) during the double-blind phase of trial 31-07-246.

The NDA submission must also include a description of the methodology and results of a literature search for new safety information with aripiprazole, in any formulation, from the cutoff date of your last comprehensive literature search to a recent date but not earlier than January 7, 2011.

We request revision of the criteria for potentially clinically relevant changes in two laboratory parameters:

1) revise the criteria for serum potassium from [REDACTED] (b) (4) mEq/L."

2) revise the criterion for a low neutrophil count from [REDACTED] (b) (4)

Additionally, for variables with both high and low criteria, such as serum potassium, please provide analyses for high and low values separately.

Also, please include an analysis of C-CASA categories in the study report for trial 31-07-246 to evaluate suicidal thoughts and behavior in the double-blind study phase. This should follow the format of the table on page 105, section 5.2, of the briefing package.

Discussion at Meeting:

The sponsor indicated that, in view of the inability to meaningfully pool the clinical studies, an ISS will not be included. Safety information will be summarized in the Clinical Safety Summary (CSS) in Module 2.7.4. Appendices will be included in Module 5 due to their large size and will be hyperlinked to the appropriate sections of the CSS. We stated that this is acceptable.

The sponsor also stated that only one adverse event (tremor) met criteria for being common and possibly drug-related in the double-blind phase of trial 31-07-246. Therefore, the demographic analysis of adverse events would be based on only this one event. We acknowledged this and indicated that no other demographic analysis of safety data was required at this time.

3. Otsuka believes that the statistical analysis plan (SAP) for the ISS, as presented in Section 5 of Appendix 3.1, is adequate to support the NDA filing and approval of aripiprazole IM depot for the maintenance treatment of schizophrenia.

Does the Division agree with the following?

- The SAP for the ISS
- The definition of “exposure” and that this definition provides sufficient exposure data for the NDA submission
- The ISS pooling plan
- The proposed format and presentation of source tables and listings in the ISS

Preliminary Comments:

As stated above, the ISS, as proposed, will not be useful in the review of safety, except to summarize exposure. The definition of exposure, i.e., based on the number of consecutive monthly injections, is acceptable but should be categorized by dose level to clearly indicate exposure at the proposed doses for clinical use, e.g., <300mg (b) (4) and 300/400mg (b) (4)

Discussion at Meeting:

No further discussion.

4. With respect to the ongoing open-label phase 3 trials (Trials 31-08-248 and 31-10-270), data from these trials will be presented as part of the pooled safety data and not as individual trial data in the ISS. However, abbreviated reports will be provided in the NDA for these trials.

Does the Division agree?

Preliminary Comments:

No, it will not be useful to pool these two trials. The safety review of data from these trials will likely be based on the abbreviated study reports supplemented by additional information that we may request for specific subjects.

Discussion at Meeting:

No further discussion.

5. The structure of the analyses data sets are provided in Appendix 4.

Does the Division agree that the structures of the analysis data sets are acceptable to support filing and approval of the NDA?

Preliminary Comments:

The datasets for potentially clinically significant laboratory values, vital sign measurements, and ECG parameters (LABCS0, VITCS0, and ECGCS0, respectively) should include the patient identifier, USUBJID. Otherwise, the datasets appear to be acceptable from a clinical standpoint to support filing of the NDA.

Discussion at Meeting:

No further discussion.

6. Otsuka proposes to include ECG data (via (b) (4)) from only the pivotal phase 3 double-blind trial (Trial 31-07-246) and the ongoing phase 3 open-label trials (Trial 31-08-248 and Trial 31-10-270) in the NDA filing.

Does the Division agree?

Preliminary Comments:

Yes, this proposal is acceptable.

Discussion at Meeting:

No further discussion.

Clinical Pharmacology

7. Otsuka believes that the PK studies conducted to date in the US (Trials CN138-020 and 31-05-244) and the ongoing population PK analyses using data from Trial 31-07-246 are adequate to support the NDA filing and approval of aripiprazole IM depot for the maintenance treatment of schizophrenia.

Does the Division agree?

Preliminary Comments:

Based on the information provided, there is also another single dose PK study (31-07-002) completed. All the studies including the pop PK analysis are needed to support the NDA filing. The results will be a matter of review.

Discussion at Meeting:

No further discussion.

8. Based upon the recent labeling change for ABILIFY® to modify dosing resulting from concomitant administration of CYP2D6 and/or CYP3A4 inhibitors, Otsuka is planning to use simulation modeling to assess transient and chronic concomitant administration of CYP2D6 and/or CYP3A4 inhibitors for aripiprazole IM depot. This evaluation will be used to provide guidance for dose adjustments.

Does the Division agree?

Preliminary Comments:

Yes, your proposed approach is acceptable. We also recommend that you simulate the worst case scenario where there is a complete dose dumping at the injection site, i.e., all the doses are dissolved and released to the systemic circulation.

Discussion at Meeting:

No further discussion.

Nonclinical

9. Otsuka will include nonclinical studies specifically conducted to support the aripiprazole IM depot formulation in the NDA. In addition, Otsuka plans to refer to nonclinical studies conducted to support the approved NDA for the oral formulation. Otsuka believes these nonclinical studies will be adequate to support the NDA filing and approval of aripiprazole IM depot for the maintenance treatment of schizophrenia.

Does the Division agree?

Preliminary Comments:

Yes, these nonclinical studies appear to be adequate to support the NDA filing; however the NDA approval is a subject of review.

Discussion at Meeting:

No further discussion.

Regulatory and Administrative

10. Products like aripiprazole IM depot for the treatment of schizophrenia are not typically used in the pediatric population. Otsuka plans to request a waiver of the requirements of the Pediatric Research Equity Act.

Does the Division agree that the justification provided supports Otsuka's plan to request a waiver of the requirements of the Pediatric Research Equity Act?

Preliminary Comments:

After submission of your NDA, your request for a waiver of PREA requirements for aripiprazole IM depot will be presented to the CDER Pediatric Review Committee (PeRC), which will render a decision on your request.

Discussion at Meeting:

No further discussion.

11. If any documents previously provided in eCTD format are referenced, they will be electronically linked to this NDA.

For modules 2.4, 2.6, and module 4, Otsuka plans to cross reference previously submitted and approved hybrid and paper NDAs as follows:

- NDA 21-436 was the primary NDA for aripiprazole (oral tablet; submitted 31 October 2001) that contained a majority of the nonclinical studies that were conducted to support the use of this drug as an oral formulation for schizophrenia.
- NDA 21-713, (submitted 20 November 2003) was a supplemental NDA submitted to the FDA for the oral solution formulation for schizophrenia.
- NDA 21-729, (submitted 22 December 2003) was a supplemental NDA submitted to the FDA for the oral disintegrating tablet formulation for schizophrenia
- NDA 21-866, (submitted 29 November 2005) was a supplemental NDA submitted to the FDA for the injectable formulation for schizophrenia and bipolar disease.

These cross references will be provided without hyperlinks or serial numbers

Does the Division agree with this method of cross referencing for the NDA?

Preliminary Comments:

From a clinical perspective, this method is acceptable. From a nonclinical perspective, we would like the cross-references (as specified in question 11) to be provided with the corresponding serial numbers.

Discussion at Meeting:

No further discussion.

12. Otsuka proposes the formatting of the draft table of contents, templates for the key tables, and figures as shown in Appendix 2 (table of contents), Appendix 3 (safety templates), and Section 5 (efficacy templates) of this briefing package.

Is this formatting acceptable to the Division?

Preliminary Comments:

Yes, the formatting is acceptable.

Discussion at Meeting:

No further discussion.

13. Otsuka proposes to submit the NDA in standard eCTD format.

Does the Division agree?

Preliminary Comments:

Yes, the standard eCTD format is acceptable.

Discussion at Meeting:

No further discussion.

14. Case report forms (CRFs) for deaths, serious adverse events, and discontinuations due to adverse events for completed and open-label trials will be included in the NDA. However, due to the potential for unblinding, CRFs for the ongoing blinded trials (Trials 31-07-247 and 031-08-003) will not be included in the NDA.

Does the Division agree?

Preliminary Comments:

CRF's for the blinded studies will not be required. However, we may request narrative summaries for specific subjects from these trials if necessary to complete our safety review.

Discussion at Meeting:

No further discussion.

15. Does the Division agree with the overall scope, content and format of the proposed NDA?

Preliminary Comments:

Please see our responses above. In addition, please note that your submission must include a demographic analysis of the primary efficacy results from trial 31-07-246.

Discussion at Meeting:

No further discussion.

Additional FDA Comments:

1. Please include the following in your future supplemental NDA submission:
 - (a) all raw as well as derived variables in .xpt format,
 - (b) the SAS programs that produced all efficacy results,
 - (c) the SAS programs by means of which the derived variables were produced from the raw variables, and
 - (d) a list of serial numbers as well as submission dates for the protocol, amendments, Statistical Analysis Plans, and relevant meetings.

Items (a) - (c) refer to efficacy variables.

Discussion at Meeting:

No further discussion.

2. We are aware of some problems with the syringe you intend to market as part of the aripiprazole IM depot kit. There have been reports of the needle/collar/syringe unit becoming loose in patients who were administered various medications using the same syringe you intend to use, in some cases resulting in the needle remaining in the patient after administration of drug and of healthcare providers being stuck with dislodged needles. We consider such incidents seriously and we need to be convinced that such problems will not occur in patients who receive aripiprazole IM depot in clinical practice, should this product ultimately be approved. Thus, you will need to demonstrate to us that the syringe/needle combination that will be distributed with your product can be safely used. We would like to know if the needle/syringe units that will be marketed are the same as those that were used in your clinical trials. If any such events occurred during the course of clinical trials, would they have been detected and reported and, if so, were any such problems detected in the course of the clinical trials? We would also like to know if there is any specific reason to use a glass syringe instead of plastic syringe for your product.

Discussion at Meeting:

(b) (4)

(b) (4) *Instead, the sponsor advised us they are exploring three kit options, all of which include the commercial drug vial, various administration components (syringes, needles, adapters), and a 5 mL vial of SWFI to reconstitute the lyophilized drug.*

We advised the sponsor to conduct a risk analysis of the three options to determine which kit configuration best suits the healthcare providers needs for safely and accurately administering the drug product in clinical practice. Of particular concern, we noted that the 5 mL vial of SWFI contains more diluent than is needed to reconstitute the drug (1.5 mL for the 300 mg vial, 1.9 mL for the 400 mg vial). Using more diluent than required could lead to overdose by allowing the overage in the vial (b) (4) to be extracted and administered. We also reiterated that it would prudent for the sponsor to reduce the overage in the vial to avoid the risk of overdoses.

We also advised the sponsor should ensure if possible that all kit components could be stored in the same conditions.

We stated that following the risk analysis and selection of the kit configuration, the sponsor should conduct a human factors study to validate that the users can safely and accurately deliver the drug as labeled. The human factors studies should be designed in accordance with the advice provided to them in the meeting held on May 9, 2011. The sponsor requested

if specific guidance on these studies is available and we referred the firm to the guidance document cited in the May 9, 2011 meeting minutes ("Medical device Use- Safety: Incorporating Human Factors Engineering into Risk Management").

We advised the sponsor that a human factors protocol could be submitted for comment in advance of conducting the study, if desired.

The sponsor indicated that they plan to provide data from the risk analysis at the time of NDA submission (targeting September 2011), but that the human factors study report would not be available at the time of NDA submission since these studies would likely be ongoing. We referred the sponsor to the advice provided in the May 9, 2011 meeting minutes regarding filing of the data with the application (see item 15(b) 1 of those minutes). The sponsor acknowledged the advice.

Conclusions:

Minutes will be provided to the sponsor. These minutes are the official minutes of the meeting. Otsuka Pharmaceuticals is responsible for notifying us of any significant differences in understanding their group has regarding the meeting outcomes.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

THOMAS P LAUGHREN

06/15/2011



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 67,380

MEETING MINUTES

Otsuka Pharmaceutical Development & Commercialization, Inc.
Attention: Suva B. Roy, Ph. D.
Senior Director, Regulatory Affairs, Quality (CMC)
2440 Research Boulevard
Rockville, Maryland 20850

Dear Dr. Roy:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Aripiprazole.

We also refer to the meeting between representatives of your firm and the FDA on September 9, 2009. The purpose of the meeting was to discuss End of Phase II, CMC topics.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-4227.

Sincerely,

{See appended electronic signature page}

Don L. Henry
Regulatory Project Manager
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure – meeting minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF NEW DRUG QUALITY ASSESSMENT

Sponsor Name:	Otsuka Pharmaceutical Development & Commercialization, Inc. (Otsuka)
Application Number:	IND 67,380
Product Name:	Aripiprazole, OPC-14597
Meeting Type:	Type B
Meeting Category:	Chemistry, Manufacturing and Controls (CMC), End of Phase 2
Meeting Date and Time:	Wednesday, September 9, 2009, 13:00 – 14:00 ET
Meeting Location:	Food and Drug Administration, White Oak Campus, Silver Spring, MD
Received Briefing Package	July 31, 2009

FDA ATTENDEES

Ramesh Sood, Ph.D, Branch Chief
Thomas Oliver, Ph.D, Pharmaceutical Assessment Lead
David Claffey, Ph.D, Quality Reviewer
Vinyak Pawar, Ph.D, Microbiologist
Angelica Dorantes, Ph.D., Biopharmaceutics Team Leader
Don Henry, Regulatory Project Manager

OTSUKA PHARMACEUTICALS ATTENDEES

Shuho Mori, M. Pharm., Associate Manager, CMC Office Medical Regulatory Affairs
Takakuni Matsuda, M. Pharm., Senior Researcher, New Formulation Project
Hiroshi Abe, Manager, B. Pharm., New Formulation Project
Yoshito Masuda, M. Pharm., Associate Director, CMC Office Medical Regulatory Affairs
Milton John Severinsen, M.Science, Manager, Quality Control and Interpreter
Hiroko Kawasaki, B.Pharm., Researcher, New Formulation Project
Shogo Hiraoka, M. Pharm., Researcher, New Formulation Project
Suva B. Roy, Ph.D., Senior Director, Regulatory Affairs, CMC

1. BACKGROUND

Otsuka Pharmaceuticals Development & Commercialization, Inc (OPC) originally marketed aripiprazole as an oral tablet (Abilify), which was approved in November 2002. Aripiprazole is also marketed as an oral solution, an orally disintegrating tablet, and an intramuscular injection. OPC has submitted an Investigation New Drug (IND) for aripiprazole as an IM Depot. This product has completed Phase 2 clinical trials. OPC has requested a meeting to discuss the chemistry, manufacturing, and controls strategy for the product.

2. DISCUSSION

- 2.1. **Briefing Package Question 1:** Does the Agency agree that the manufacture of sterile aripiprazole monohydrate (b) (4)

(b) (4) Does the Agency agree and the sterile aripiprazole monohydrate is an (b) (4) material?

FDA Response: *The Agency does not agree with this approach. The aripiprazole monohydrate should be considered the final drug substance and all information pertaining to the chemistry, manufacturing and controls needs to be included in the drug substance section of the application. The CMC information related to the anhydrous material can be cross referenced to other NDA(s).*

Meeting Discussion: There was no further discussion on this topic.

- 2.2. **Briefing Package Question 2:** In order to establish equivalency of the drug products manufactured with (b) (4)

(b) (4)

Does the Agency agree with the adequacy of this data set?

FDA Response: *The Agency agrees with this general approach, provided that the dissolution method is found discriminatory to detect differences in the dissolution of*

(b) (4)

Meeting Discussion: There was no further discussion on this topic.

- 2.3. **Briefing Package Question 3:** Does the Agency agree with the proposed data set for registration of (b) (4) as the manufacturing site for sterile aripiprazole monohydrate (b) (4)?

FDA Response: *The Agency agrees with this approach.*

Meeting Discussion: There was no further discussion on this topic.

- 2.4. **Briefing Package Question 4:** Does the Agency agree with the proposed data set for registration of Otsuka Pharmaceutical Second Tokushima Factory as the second manufacturing sites for sterile aripiprazole monohydrate in-process material?

FDA Response: *The Agency agrees with this approach.*

Meeting Discussion: There was no further discussion on this topic.

- 2.5. **Briefing Package Question 5:** Does the Agency agree with this strategy for qualifying the equipment changes and establishing the equivalency between the primary stability batches (i.e., LTSS batches) and the commercial production batches?

FDA Response: *We remind you that the primary stability batches need to be representative of the commercially manufactured product (e.g. manufacturing process, filling, packaging). Refer to ICH Q1A(R2) for stability guidance. Additionally, ensure that the levels of other polymorphic forms (b) (4) (b) (4) are controlled and evaluated as part of the equipment changes.*

Meeting Discussion: There was no further discussion on this topic.

- 2.6. **Briefing Package Question 6:** Does the Agency agree with the proposed sterilization validation and sterile processing data set for the sterile aripiprazole monohydrate in process material and the IM Depot drug product?

FDA Response: *The Agency agrees with the approach.*

Meeting Discussion: There was no further discussion on this topic.

- 2.7. **Briefing Package Question 7:** Does the Agency agree with the proposed provisional specifications for the sterile aripiprazole monohydrate and the commercial Aripiprazole IM Depot injection?

FDA Response: *For aripiprazole monohydrate, we recommend the addition of a test and an acceptance criterion for the (b) (4). We recommend that you evaluate the effect of particle size of the monohydrate on the drug product and determine whether a control is needed in the drug substance specification. All other attributes are acceptable; however, the acceptability of the criteria will be determined during the NDA review process.*

For the drug product we recommend:



- f. *Include the following tests or justify the absence of:*
- i. *Maximum Injection Force required for administering the dose.*
 - ii. *Suspension viscosity.*
 - iii. *Morphology of the aripiprazole (b) (4)*
 - iv. *Deliverable volume.*

The acceptability of the criteria will be determined during the NDA review process.

Meeting Discussion: With regards to particle size distribution (item c), the Agency indicated that as part of the NDA submission, the data should be presented in graphical form, depicting all clinical lots and any other lots manufactured prior to the submission. This data will be evaluated to determine whether the proposed specification has been appropriately established. To clarify

the criteria for the (b) (4), the limit should be re-written (e.g., no more than (b) (4)).

Regarding injection force, refer to ISO 7886-1 Sterile Hypodermic Syringes for Single Use - Part 1: Syringes for Manual Use

For deliverable volume, Otsuka indicated they are pursuing the product as a single vial with a separate WFI source, and as a kit with prepackage WFI source. The Agency indicated that for both options, data needs to be provided during the NDA submission that demonstrates the proposed overfill is adequate to consistently deliver the full dose to the patient. If the kit option is presented and the prepackage WFI source is commercially available, Otsuka will need to ensure that the volume of the WFI will not permit multiple use of the product. Additionally, you are reminded that the expiration date of the product will be determined by the component with the earliest expiry date.

If the kit with a syringe option is presented during the submission, Otsuka will need to provide data to support the use of the syringe.

- 2.8. **Briefing Package Question 8:** Does the Agency agree with the proposed stability study protocols and stability data package for aripiprazole IM Depot drug product?

FDA Response: *The approach is acceptable; however, the primary stability batches need to be representative of the commercially manufactured product (e.g. manufacturing process, filling, packaging). Refer to ICH Q1A(R2) for stability guidance. We recommend that the additional tests described in response to Question 7 be considered for inclusion in the stability protocol.*

Meeting Discussion: There was no further discussion on this topic.

- 2.9. **Briefing Package Question 9:** Does the Agency agree that the drug product expiry can be calculated from the time when sterile aripiprazole is mixed with the vehicle in the manufacture of the drug product?

FDA Response: *The Agency agrees with the approach.*

Meeting Discussion: There was no further discussion on this topic.

- 2.10. **Briefing Package Question 10:** Does the Agency agree with the stability protocol and the proposed stability data package for the sterile in-process aripiprazole monohydrate from (b) (4)?

FDA Response: *We generally agree with this approach. As was stated above we recommend that you include a quantitative limit for the (b) (4) in the specification.*

Meeting Discussion: There was no further discussion on this topic.

- 2.11. **Briefing Package Question 11:** Does the Agency agree with the stability protocol and the proposed stability data package for the sterile in-process aripiprazole monohydrate from Otsuka Second Tokushima factory? Does the Agency agree with strategy?

FDA Response: *The Agency agrees with the approach.*

Meeting Discussion: There was no further discussion on this topic.

- 2.12. **Briefing Package Question 12:** Does the Agency agree with the proposed additional stability study protocols and stability data package for aripiprazole IM Depot drug product?

FDA Response: *The Agency agrees with the approach.*

Meeting Discussion: There was no further discussion on this topic.

- 2.13. **Briefing Package Question 13:** Does the Agency agree that the expiry dating from the stability data obtained from batches manufactured with the current equipment can be extended to the product made with updated (b) (4) based on the batch analysis data included in the initial NDA and satisfactory 6-month stability data submitted with the stability update during the NDA review?

FDA Response: *The Agency agrees with the approach, however, this will be a review matter. We remind you that all updated stability data will need to be submitted by mid-cycle.*

Meeting Discussion: There was no further discussion on this topic.

- 2.14. **Briefing Package Question 14:** Does the Agency agree that the data package is adequate to propose 2-year hold period for both (b) (4) and Second Tokushima Factory?

FDA Response: *As previously mentioned, the aripiprazole monohydrate is considered the final drug substance, and therefore, a hold period is not applicable.*

Meeting Discussion: The drug substance will have an assigned retest dating period and the drug product will be assigned an expiration dating period.

- 2.15. **Briefing Package Question 15:** Does the Agency agree that the proposed data package is adequate to support the pre-filled syringe?

FDA Response: *This is a post-approval change that will be evaluated at the time of the supplement submission.*

Meeting Discussion: There was no further discussion on this topic.

3. ADDITIONAL COMMENTS/ISSUES REQUIRING FURTHER DISCUSSION

- 3.1. We request that data on the solubility of aripiprazole hydrate in whole blood and blood plasma be provided.
- 3.2. We request that any issues encountered during clinical studies with drug product reconstitution or administration be mentioned in the CMC section of the NDA.
- 3.3. Recommendation for dissolution method development and validation report

Dissolution Method Development

We recommend that the following information generally be included in the dissolution method development report:

- The pH solubility profile of the drug substance
- Dissolution profiles generated at different agitation speeds
- Dissolution profiles generated in at least three media
- Dissolution profiles generated in different testing apparatus
- Factors that affect the dissolution rate of the suspension, i.e., particle size, (b) (4) and concentration of the suspended drug should be investigated

It is recommended that the sponsor select the agitation speed, medium, and apparatus that provide adequate discriminating ability, taking into account all the available in-vitro and in-vivo data.

For the development of the dissolution testing conditions, such as apparatus, dissolution medium, and rotation speed, the following recommendations may be considered:

- Dissolution methodologies and apparatus described in the USP can generally be used. In general, most of the dissolution apparatus that have been described for tablets and capsules can easily be utilized for suspensions. However there are other alternatives that may be considered. For example, (b) (4)
(b) (4)
- The testing conditions should be based on physicochemical characteristics of the drug substance and the environmental conditions the dosage form might be exposed to after administration.
- The volume of the dissolution medium is generally (b) (4) conditions are desirable but not mandatory. A surfactant may be used with appropriate justification.
- In general, (b) (4) conditions should be maintained during dissolution testing to allow maximum discriminating power and to detect products with poor in vivo performance.

The data assessed to set the specification are generally obtained from batches that have been used in pivotal clinical and/or bioavailability studies and from other human studies conducted during product development.

For setting the dissolution specifications, dissolution profiles of at least 12 individual dosage units from each lot should be determined. A suitable distribution of sampling points should be selected to define adequately the entire dissolution profile. It is important to characterize the early stage of the dissolution profile to assure against premature release of the drug (dose dumping) from the formulation, and the late stage to assure a plateau is reached). Although there is no requirement for 100% dissolution in the profile, the infinity point can provide data that may supplement content uniformity data and may provide useful information about formulation characteristics or about method bias. The last time point should be the time when a plateau of the dissolution profile has been reached.

The percentage of labeled claim dissolved at each specified testing interval should be reported for each individual dosage unit. The mean percent dissolved, range (highest and lowest) of dissolution, and coefficient of variation (relative standard deviation) should be tabulated. The coefficient of variation (CV) for mean dissolution profiles of a single batch should be less than 10%.

A graphic representation of the mean dissolution profiles should also be included.

Specifications should be established based on average dissolution data for each lot under study, equivalent to USP Stage 2 testing. Specifications that allow all lots to pass at Stage 1 of testing can be wide and may result in lots with less than optimal in vivo performance to pass these specifications at USP Stage 2 or Stage 3.

Method Validation

We recommend that the following information generally be included in the method validation report:

- System suitability test and all appropriate steps and procedures of analytical methods validation.
- Validation between manual and automated procedures
- Validation of a determinative step (i.e., analytical methods employed in quantitative analysis of dissolution samples). It should include summaries of experimental data and calculations substantiating each of the applicable analytical performance characteristics. Typical Analytical Characteristics used in method validation are: accuracy, precision, specificity, detection limit, quantitation limit, linearity, range, and robustness.
- Content uniformity test

Additional Meeting Discussion:

1. The Agency reminds you that the agglomeration as a function of time needs to be evaluated and presented as part of the NDA submission.
2. The dissolution profile data from page 82 needs to be clarified and presented in the dissolution report.
3. Otsuka indicated that the proposed equipment changes (b) (4) will be part of the NDA submission and the validation data will be included. The (b) (4) syringe is in early development stages and would be pursued as a post-approval change.
4. If the kit with a syringe option is pursued, a combination product designation (i.e. drug and device) will be determined by the clinical division. Clearly, utilizing a syringe which has not been approved in the United States would require more information than the utilization of an approved syringe. Regardless of the designation, the Center for Devices and Radiological Health (CDRH) will be consulted.

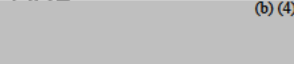

4. CONCURRENCE:

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-67380	GI-1	OTSUKA PHARMACEUTICA L DEVELOPMENT AND  (b) (4)	OPC-14597
IND-67380	GI-1	OTSUKA PHARMACEUTICA L DEVELOPMENT AND  (b) (4)	OPC-14597

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/s/

RAMESH K SOOD
09/14/2009